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American Journal of OBSTETRICS AND GYNECOLOGY

Editors

HOWARD C. TAYLOR, JR. WILLIAM J. DIECKMANN

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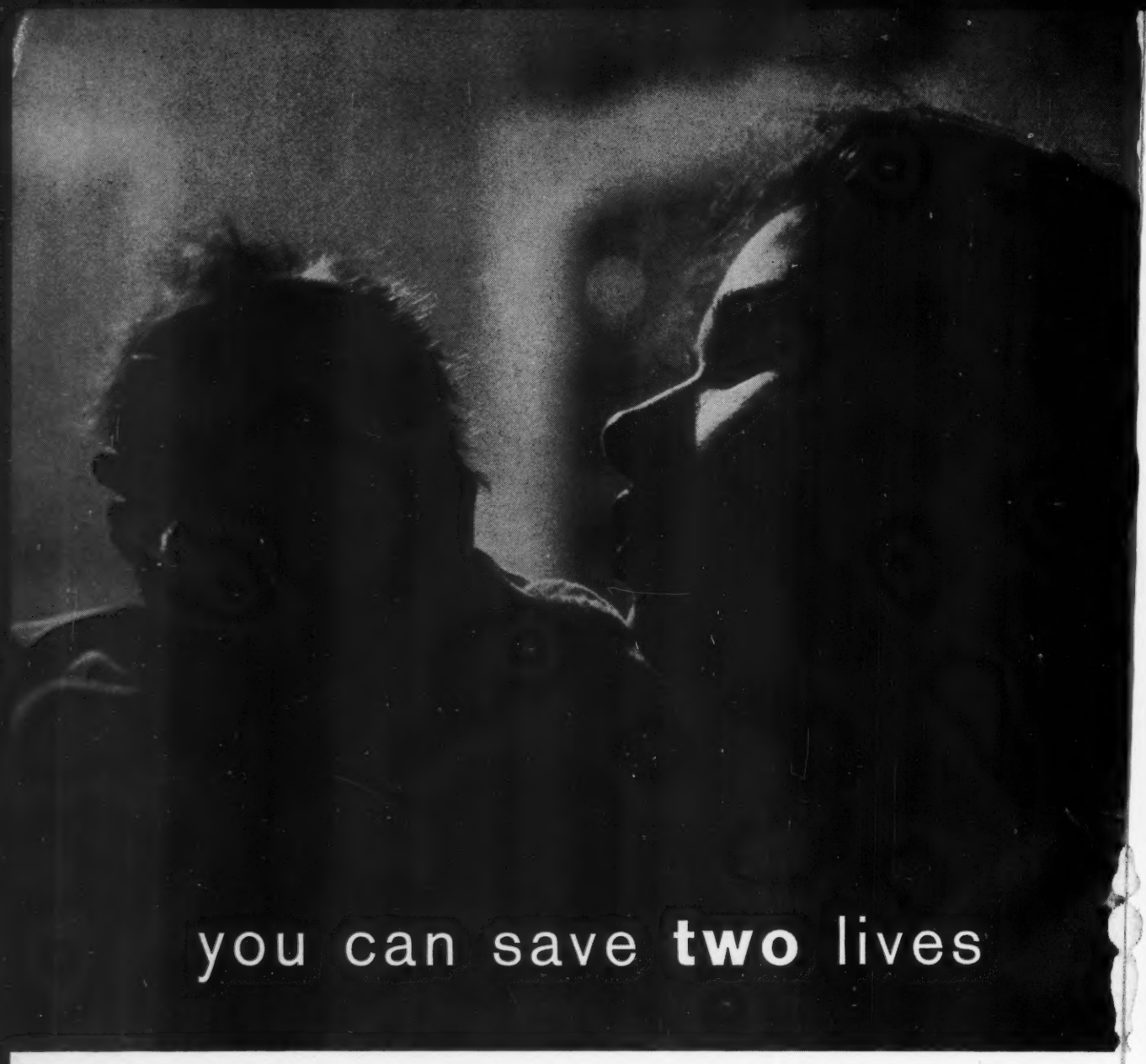

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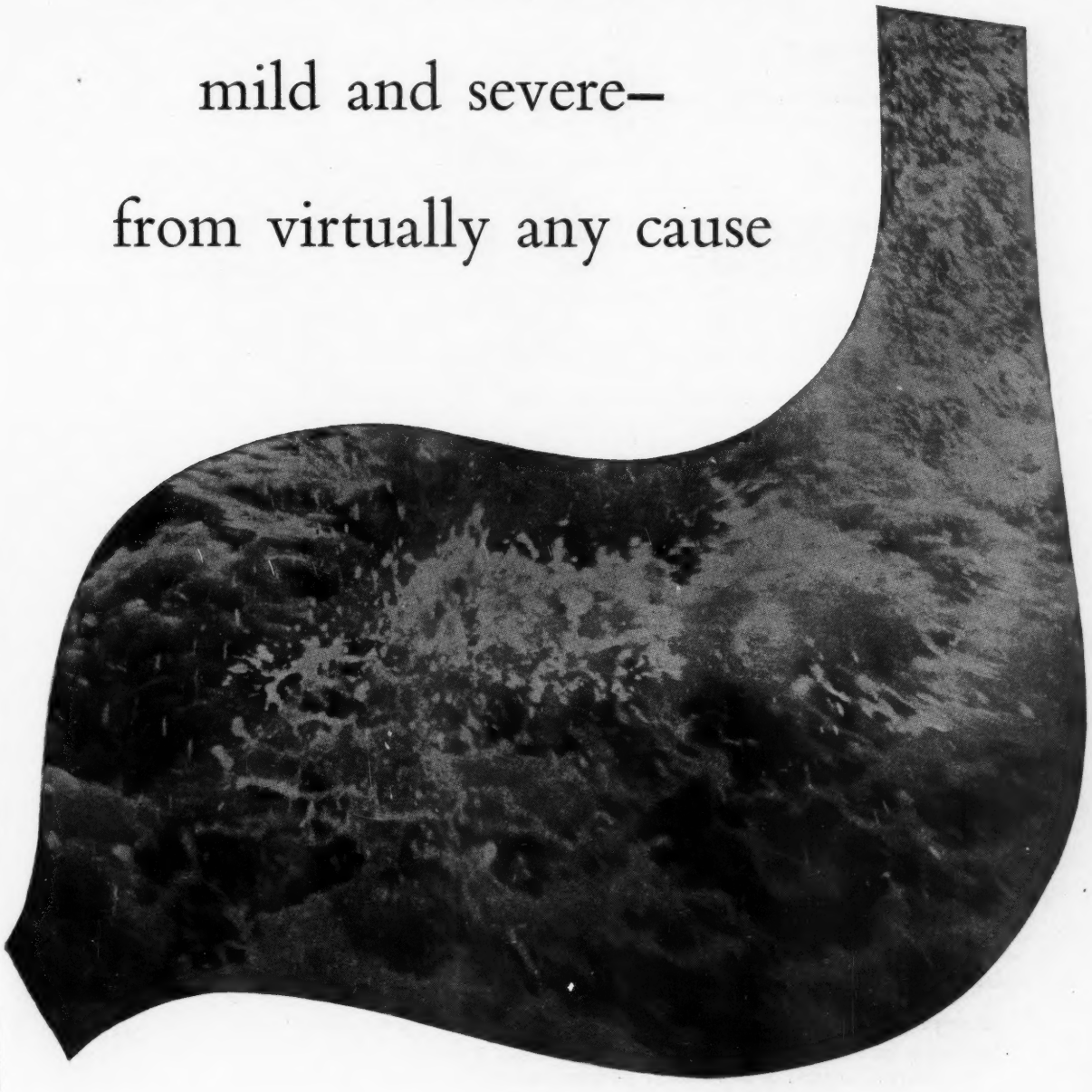

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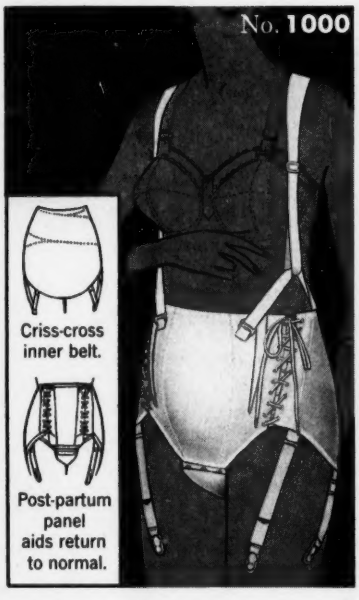

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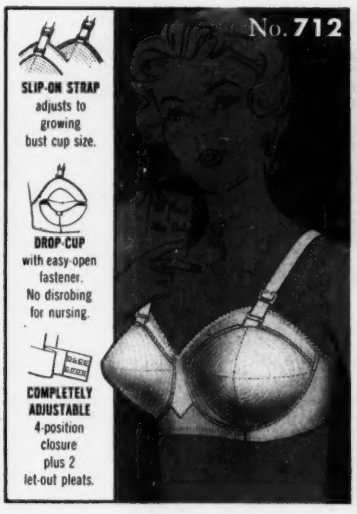
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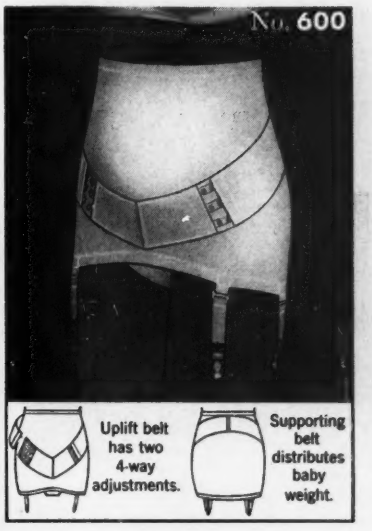

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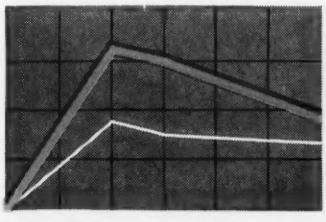


ACTIVATED TETRACYCLINE THERAPY FOR HIGHER, FASTER BLOOD LEVELS PROVIDES POTENT, PROMPT, PROLONGED CONTROL OF TETRACYCLINE-SUSCEPTIBLE INFECTIONS

TETRABON® V

TETRACYCLINE-PHOSPHATE BUFFERED

homogenized syrup

Orange-flavored, specially homogenized liquid preparation of activated tetracycline assures faster, higher levels of broad-spectrum therapy and assures acceptance by patients of all ages.

Supplied: Each 5 cc. teaspoonful of Tetrabon V contains tetracycline equivalent to 125 mg. tetracycline hydrochloride, phosphate buffered.
Bottles of 2 oz. and 1 pint, ready to use.

1. Welch, H.; Lewis, C. N.; Staffa, A. W., and Wright, W. W.: Antibiotic Med. & Clin. Therapy 4:215 (April) 1957.

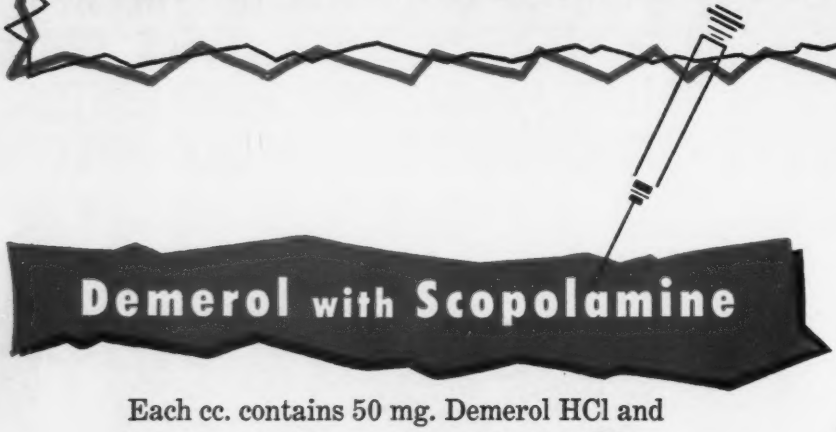
INFLUENZA patients and those with minor respiratory tract infections can get prompt symptomatic relief and protection or treatment of secondary bacterial complications with TETRACYDIN® Tablets (tetracycline-analgesic-antihistamine).

Pfizer

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.
WORLD LEADER IN ANTIBIOTIC DEVELOPMENT AND PRODUCTION

For Your Convenience

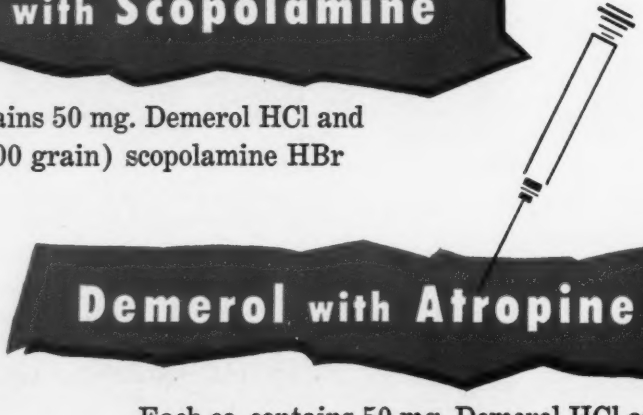
2 NEW Parenteral DEMEROL® COMBINATIONS



Demerol with Scopolamine

Each cc. contains 50 mg. Demerol HCl and
0.2 mg. (1/300 grain) scopolamine HBr

Vials of 30 cc.



Demerol with Atropine

Each cc. contains 50 mg. Demerol HCl and
0.2 mg. (1/300 grain) atropine sulfate

Ampuls of 2 cc., boxes of 25

Subject to regulations of the Federal Bureau of Narcotics.

Winthrop LABORATORIES
NEW YORK 18, N. Y.

Demerol (brand of meperidine), trademark reg. U.S. Pat. Off.

diagnosis
without
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Salpix®
contrast medium

in hysterosalpingography
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Ortho Pharmaceutical Corporation
RARITAN, NEW JERSEY

Ortho

for certain disorders of menstruation and pregnancy

TRULY EFFECTIVE PROGESTATIONAL THERAPY BY MOUTH

NORLUTIN

T.M.

(norethindrone, Parke-Davis)

oral progestogen with unexcelled potency and unsurpassed efficacy

Now, with small oral doses of this new and distinctive progestogen, you can produce the clinical effects of injected progesterone. In amenorrheic women for example, "As little as 50 mg. of [NORLUTIN] administered in divided doses over a five-day period was sufficient to induce withdrawal bleeding."[1]

CASE SUMMARY[2]

Amenorrhea of 4 years' duration in a 24-year-old married woman. A course of 10 mg. NORLUTIN twice daily for 5 days was followed after 3 days by menses lasting about 5 days. Since no spontaneous menstruation occurred during the following 35 days, she was given another course of treatment with NORLUTIN, 10 mg. twice daily for 5 days. This was followed by menses.

When this patient was given ethisterone, 40 mg. twice daily for 5 days, no bleeding had ensued when she was seen 41 days later.

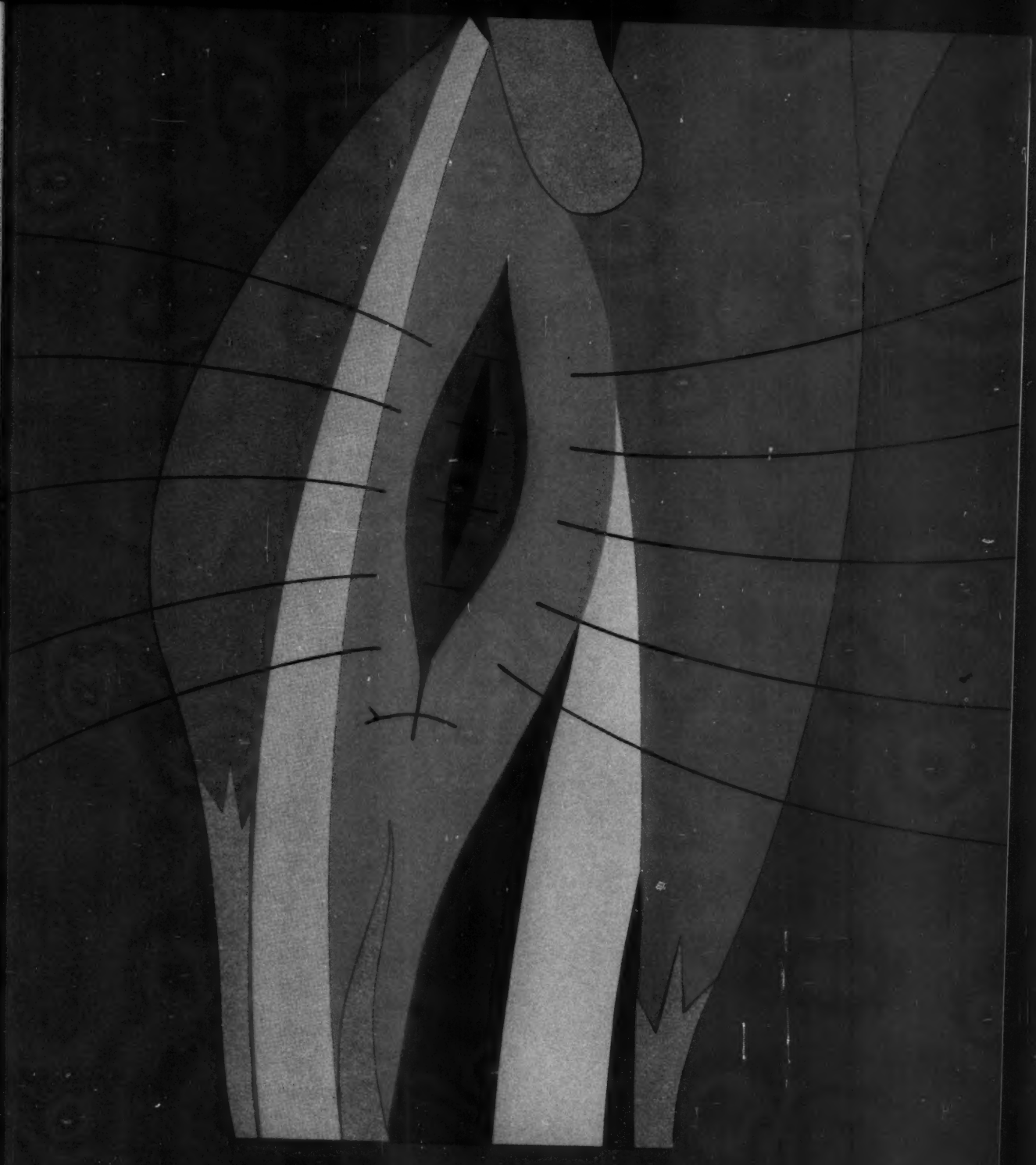
INDICATIONS FOR NORLUTIN: conditions involving deficiency of progestogen such as primary and secondary amenorrhea, menstrual irregularity, functional uterine bleeding, endocrine infertility, habitual abortion, threatened abortion, premenstrual tension, and dysmenorrhea.

PACKAGING: 5-mg. scored tablets (C. T. No. 882), bottles of 30.

REFERENCES: (1) Greenblatt, R. B.: *J. Clin. Endocrinol.* 16:869, 1956. (2) Hertz, R.; Waite, J. H., & Thomas, L. B.: *Proc. Soc. Exper. Biol. & Med.* 91:418, 1956.

MEDICAMENTA VERA

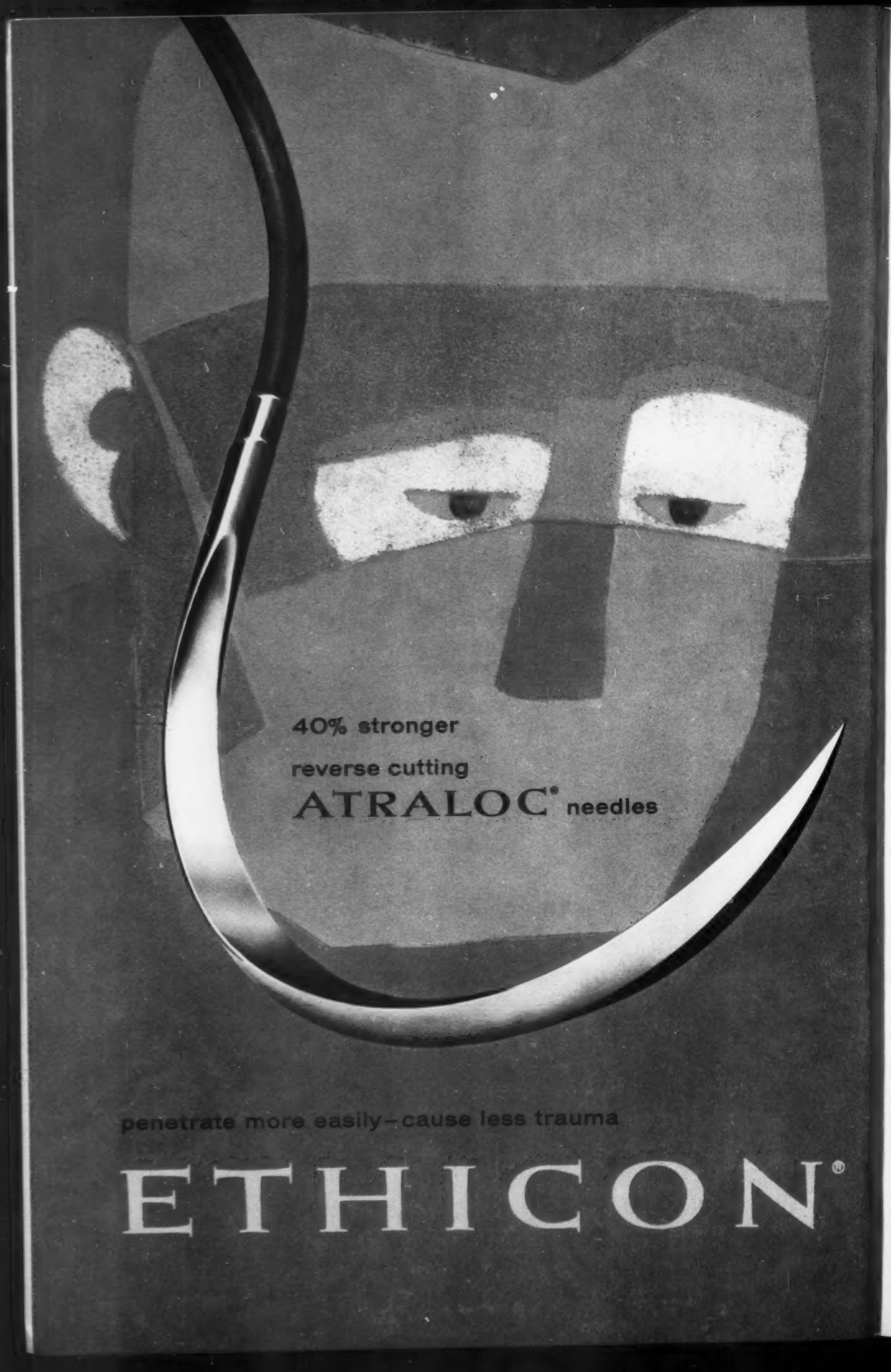
PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

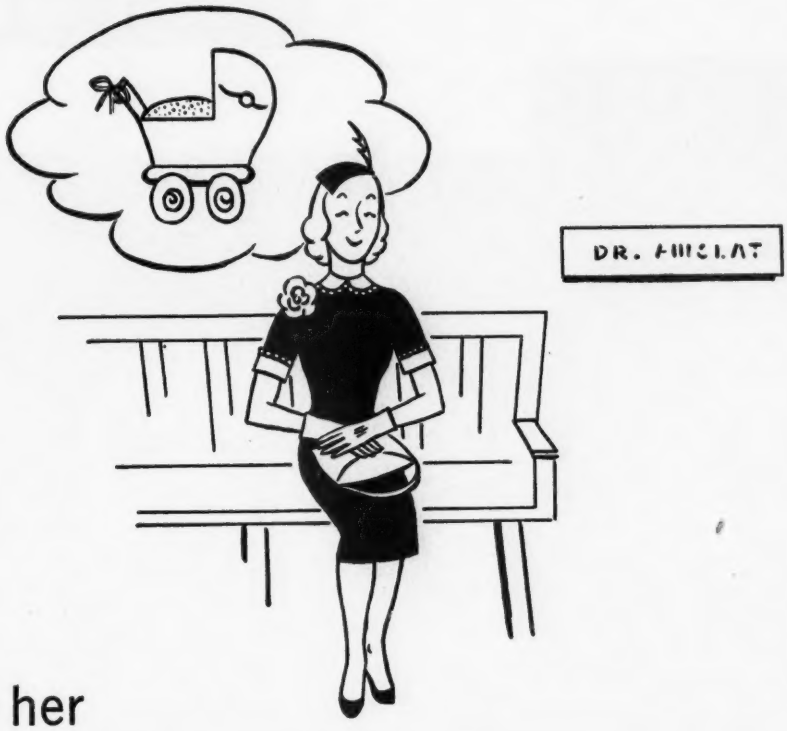


setting new standards

ETHICON®

sutures


40% stronger
reverse cutting
ATRALOC® needles
penetrate more easily–cause less trauma
ETHICON®



assure her

a more serene, a happier pregnancy
. . . without nausea

give her **'MAREDOX'®** brand

Cyclizine Hydrochloride and Pyridoxine Hydrochloride

because 'Maredox' gives the expectant mother new-found relief from morning sickness.

relieves nausea and vomiting and ***counteracts pyridoxine deficiency*** — *in pregnancy*

One tablet a day, taken either on rising or at night, is all that most women require.

Each tablet of 'Maredox' contains:
'Marezine'® brand Cyclizine Hydrochloride..... 50 mg.
Pyridoxine Hydrochloride ..... 50 mg.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

NO WITHDRAWAL BLEEDING

Vallestril® relieved symptoms in 91 per cent of menopausal patients

Physicians are aware of the anxiety caused when bleeding occurs during menopausal therapy. According to Goldfarb and Napp, "for this reason, as well as the possibility of masking carcinoma, the great advantage of methallenestril [Vallestril] lies in the absence of bleeding during therapy or on discontinuance of treatment with this drug."*

Attending this unique therapeutic advantage, these investigators observed that relief of symptoms with Vallestril occurred in 91 per cent of 100 menopausal patients.

Administration—For the menopausal syndrome two 3-mg. tablets (6 mg.) of Vallestril should be taken daily for three weeks; thereafter, to control symptoms 3 mg. daily for as long as required. G. D. Searle & Co., Chicago 80, Illinois. Research in the Service of Medicine.

*Goldfarb, A. F., and Napp, E. E.: Use of Methallenestril (Vallestril) in Control of Menopausal Symptoms, J.A.M.A. *161*:616 (June 16) 1956.

SEARLE

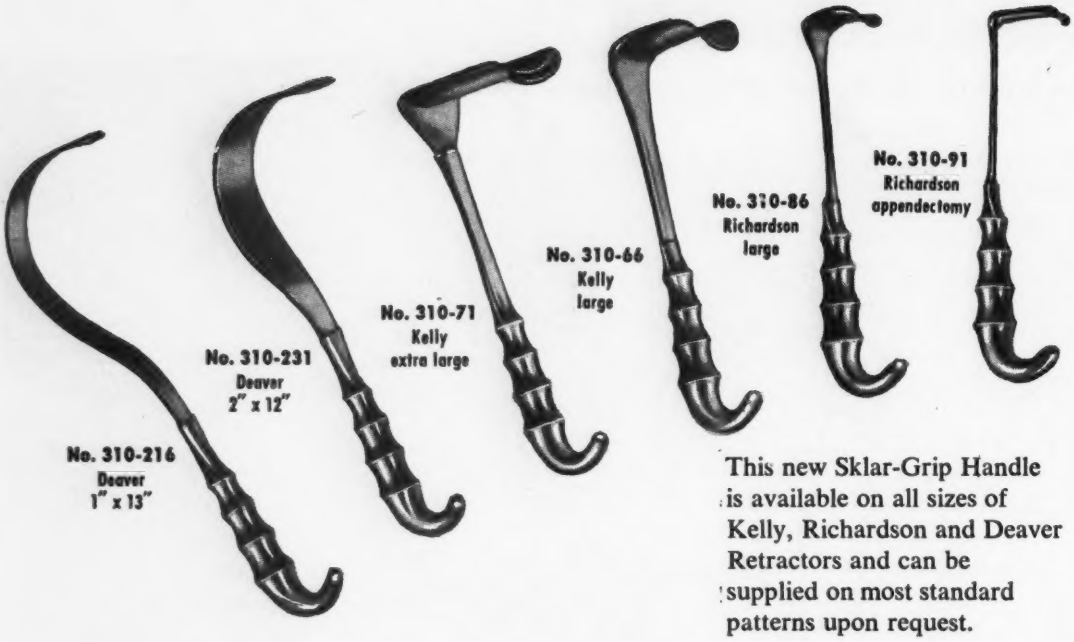
In Ireland, too, Pentothal is used almost constantly

**Unmistakably
the world's most widely studied
intravenous anesthetic**

With PENTOTHAL Sodium, there is no prolonged induction period. Recovery is smooth, rapid, because there is little drug to be detoxified. And PENTOTHAL is economical because the *total* dosage to achieve the desired levels of anesthesia is small. More than 2700 published reports, over 23 years of use . . . make it an "agent of choice" wherever modern intravenous anesthesia is practiced. Abbott

PENTOTHAL® Sodium

(Thiopental Sodium for Injection, Abbott)



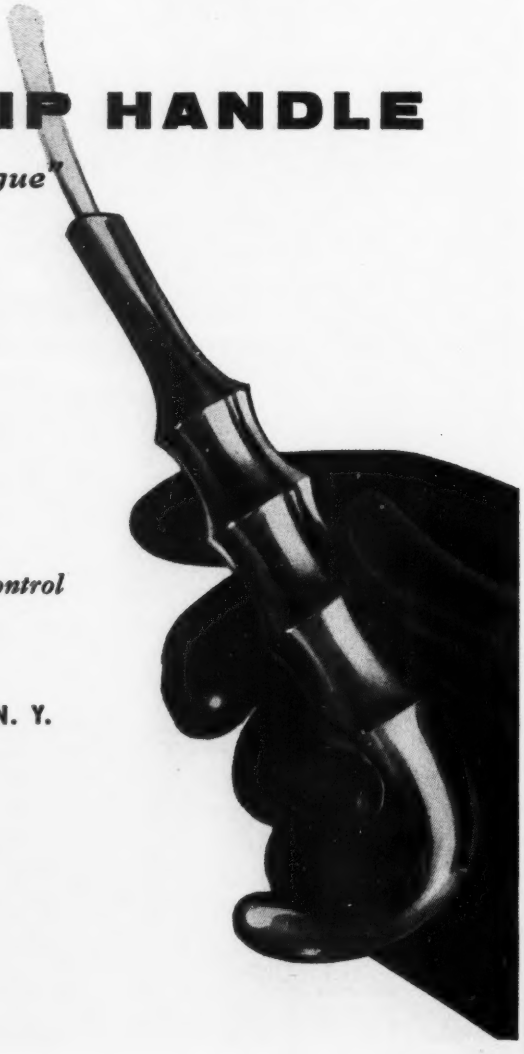
This new Sklar-Grip Handle is available on all sizes of Kelly, Richardson and Deaver Retractors and can be supplied on most standard patterns upon request.

New...

SKLAR-GRIP HANDLE

Answer to "Retractor Fatigue"

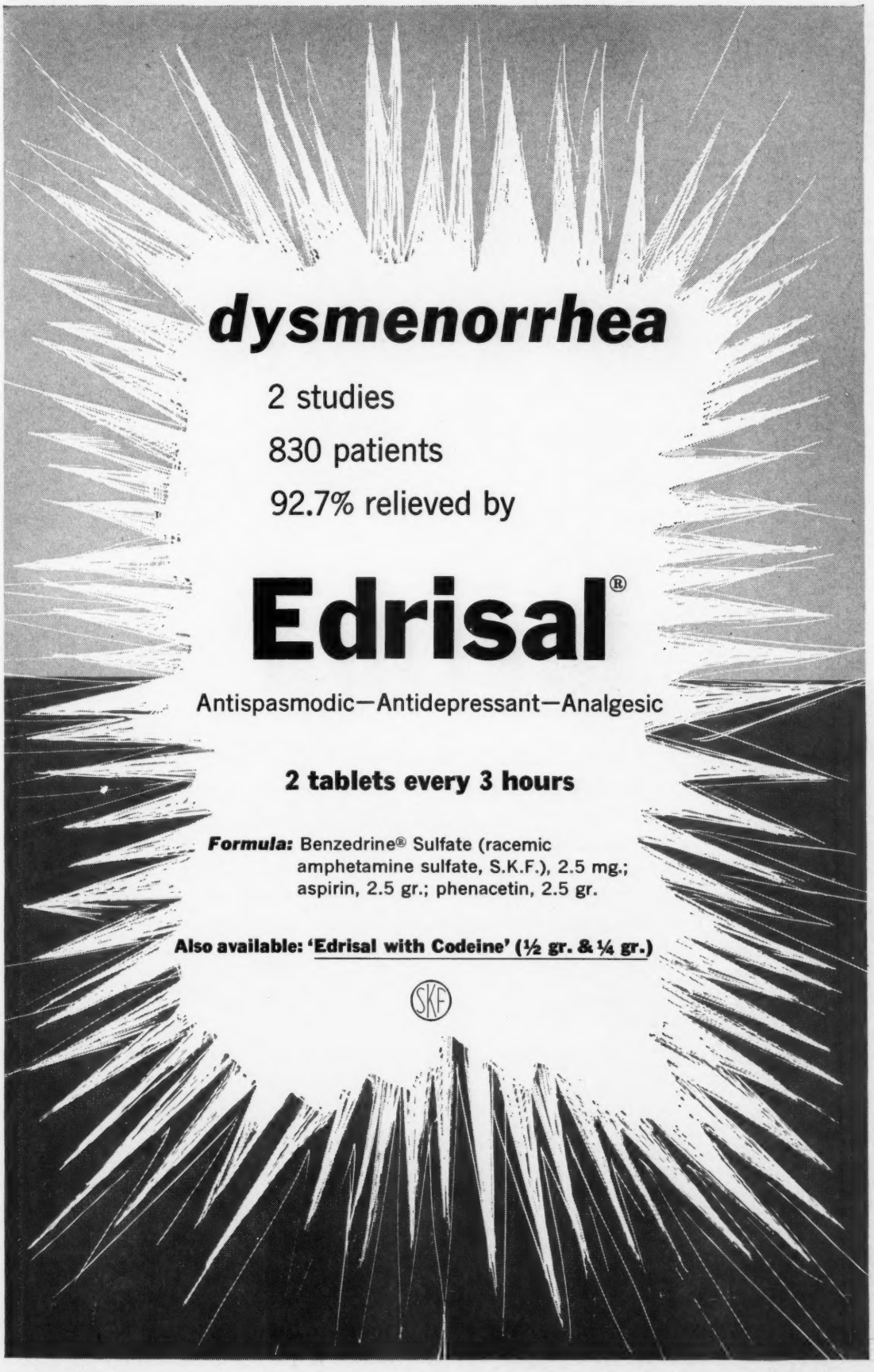
The new Sklar-Grip follows the contour of any hand. This modification assures exceptional comfort and control during any surgical maneuver, particularly where prolonged retraction is indicated.



The Sklar-Grip Handle . . .
Easy to hold . . .
A new experience in balance and control

Sklar LONG ISLAND CITY, N. Y.

CAUTION: If the name SKLAR is not stamped on the instrument it is not a genuine Sklar Product.


dysmenorrhea
2 studies
830 patients
92.7% relieved by
Edrisal®
Antispasmodic—Antidepressant—Analgesic
2 tablets every 3 hours
Formula: Benzedrine® Sulfate (racemic amphetamine sulfate, S.K.F.), 2.5 mg.; aspirin, 2.5 gr.; phenacetin, 2.5 gr.
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IMPORTANT THERAPY

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Specific Topical Benefits

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Pruritus Vulvae Et Ani
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Hist-A-Cort-E™ pH 4.7

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INCORPORATED IN EXCLUSIVE ACID MANTLE® VEHICLE

ACID MANTLE® Hydrocortisone–
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Epithelium Regenerative
Antiinflammatory
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Sig: Apply twice daily—Supply: 1 oz. tubes

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"this is it for today"...

now...
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ENGRAN Term-Pak

—containing 250 Engran tablets... enough for the full term... in a reusable jar—plus a convenient purse-size tablet dispenser

Just 1 Engran daily helps to assure a nutritionally perfect pregnancy

Engran tablets are • small • easily swallowed • money saving

Each capsule-shaped Engran tablet supplies:	
Vitamin A	5000 U.S.P. Units
Vitamin D	500 U.S.P. Units
Vitamin K (as menadione)	0.5 mg.
Thiamine mononitrate	3 mg.
Riboflavin	3 mg.
Pyridoxine HCl	2 mg.
Vitamin B_{12} Activity concentrate	2 mcg.
Folic acid	0.25 mg.
Niacinamide	20 mg.
Calcium pantothenate	5 mg.
Ascorbic acid	75 mg.
Calcium, elemental (as calcium carbonate, 375 mg.)	150 mg.
Iron, elemental (as ferrous sulfate exsic., 33.6 mg.)	10 mg.
Iodine, elemental (as potassium iodide, 0.2 mg.)	0.15 mg.
Potassium (as the sulfate)	5 mg.
Copper (as the sulfate)	1 mg.
Magnesium (as the oxide)	6 mg.
Manganese (as the sulfate)	1 mg.
Zinc (as the sulfate)	1.5 mg.

Bottles of 100, 250 and 1000.

Engran

Squibb Vitamin-Mineral Supplement

SQUIBB *Squibb Quality—the Priceless Ingredient*

'ENGRAN'® IS A SQUIBB TRADEMARK

A "sense of well-being" is an added benefit in "Premarin" therapy

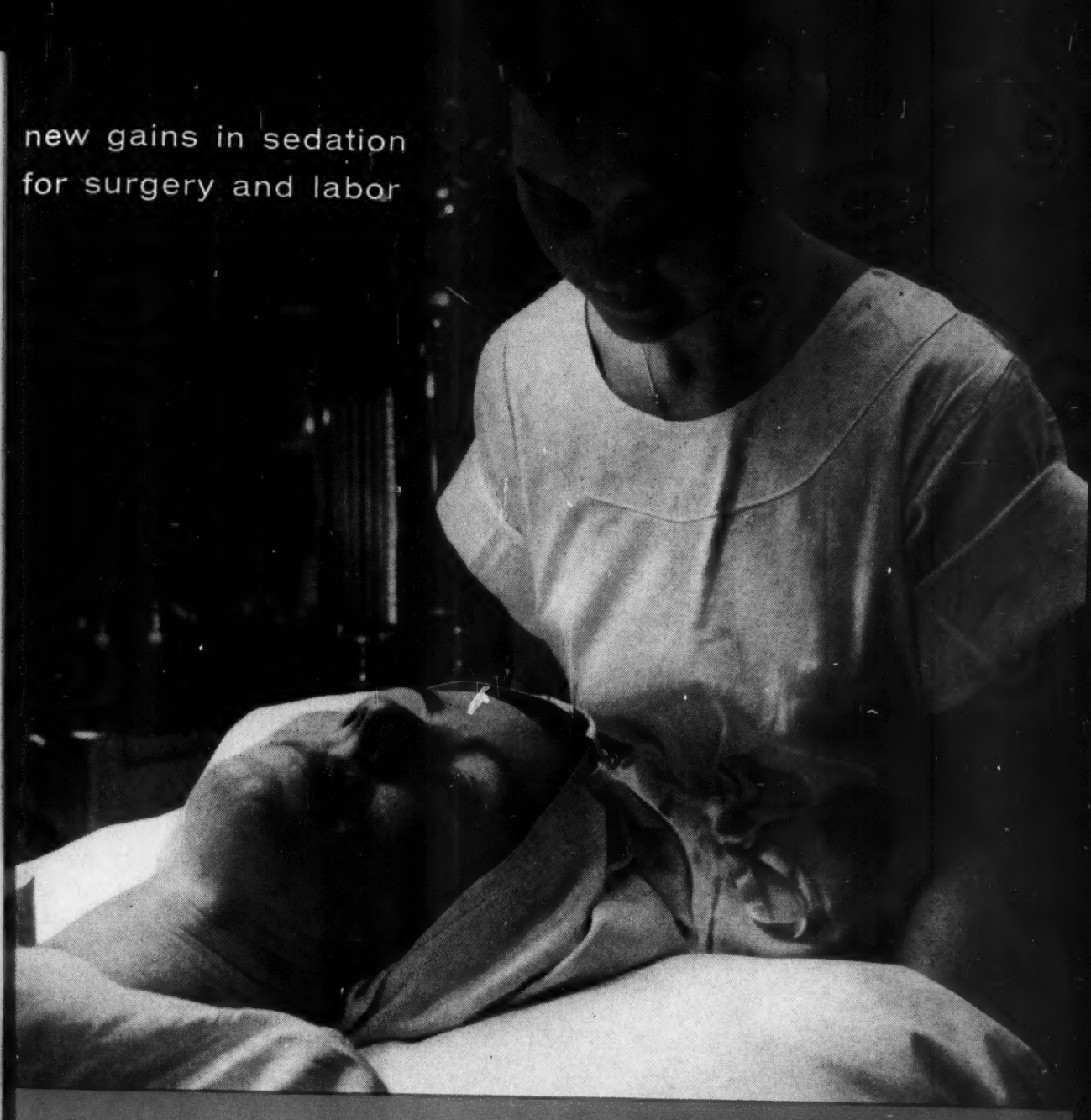
Every woman who suffers in the menopause deserves "Premarin," widely used natural, oral estrogen.

"Premarin" produces prompt symptomatic relief and a gratifying "sense of well-being." "Premarin" presents the complete equine estrogen-complex. Has no odor, imparts no odor.

"PREMARIN"®
Conjugated estrogens (equine)

in the menopause and the pre- and postmenopausal syndrome

5642 Ayerst Laboratories • New York, N. Y. • Montreal, Canada



QUIESCENCE
...not depression

1. Relieves apprehension without blocking perception or depressing the vital functions
2. Promotes composure and cooperation
3. Induces light sleep with easy awakening
4. Controls nausea and vomiting both prophylactically and therapeutically
5. Reduces analgesic and sedative requirements

Comprehensive literature is available on request.

Wyeth®
Philadelphia 1, Pa.

PHENERGAN®
HYDROCHLORIDE
Promethazine Hydrochloride

INJECTION
TABLETS
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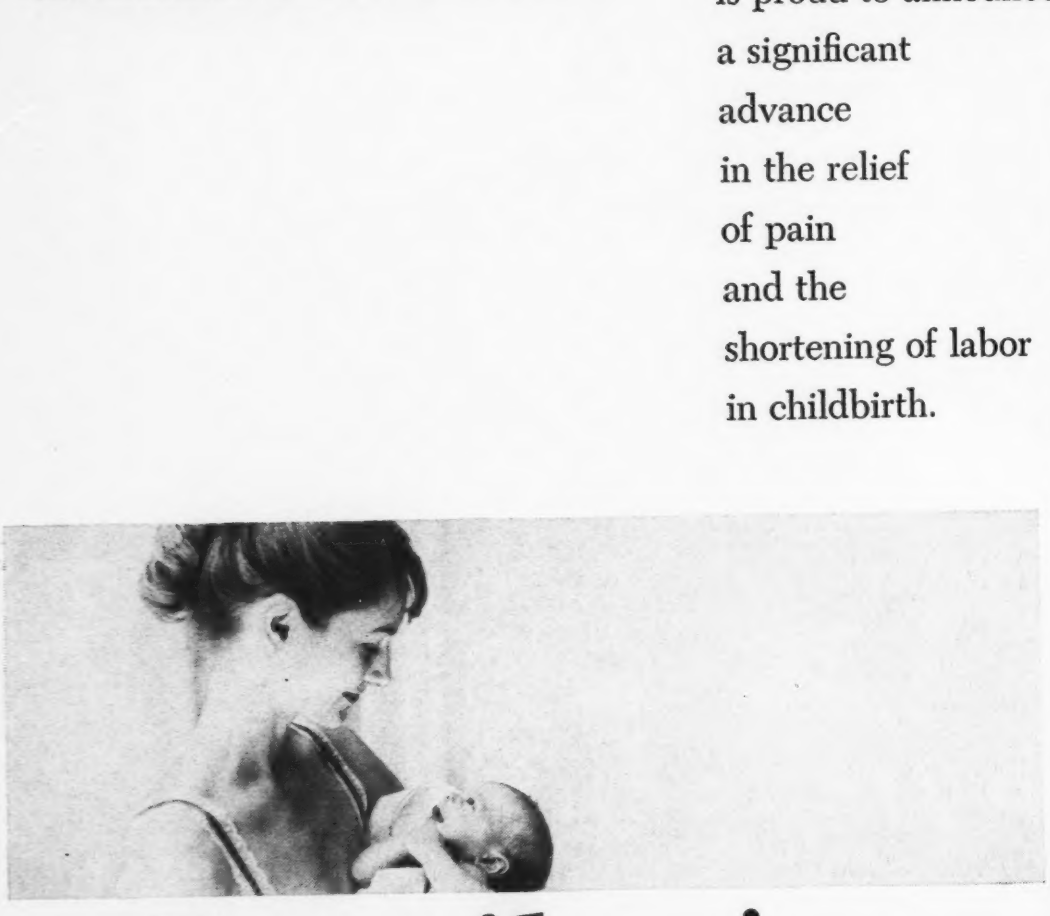
Easier Childbirth

The National Drug Company is proud to announce a significant advance in the relief of pain and the shortening of labor in childbirth.



Cervilaxin®

NATIONAL brand of relaxin

for shorter labor, ...easier delivery

Answers to some questions on Cervilaxin[1,2]

Q. What is Cervilaxin?

A. Cervilaxin is a new, highly purified form of relaxin, a hormone normally produced at term.

Q. When is it indicated?

A. Cervilaxin is of value in frank labor with slow cervical dilatation, and, with oxytocin, for induction of labor and uterine dysfunction.

Q. What are its advantages?

A. Cervilaxin eases and shortens labor (see Fig. 1): less pain, less trauma, less need for intervention. It lessens danger of fetal damage (brain injury).

Cervilaxin makes oxytocin safer since there is less likelihood of uterine rupture or other adverse effects.

Q. How does it act?

A. Cervilaxin softens the cervix so that it offers less resistance to passage of the fetus; dilatation is facilitated.

Q. Is Cervilaxin recommended for controlling premature labor?

A. No. In massive doses Cervilaxin may retard uterine contractions and prevent premature birth, but this effect is not evident in the smaller doses recommended here.

Q. Is Cervilaxin indicated only in primiparas?

A. No, Cervilaxin has been used with good results in primiparas, and in multiparas with a history of previous difficult labor.

Q. Does Cervilaxin interfere with necessary uterine contractions during labor?

A. No. In recommended dosage there is no interference with well established, regular and normal physiological functions before, during, or after delivery.

Q. What effect does Cervilaxin have on other drugs given during delivery?

A. Cervilaxin does not interfere with the action of any of the drugs commonly employed before, during, or after delivery.

Q. What side effects have been observed?

A. To date, none.

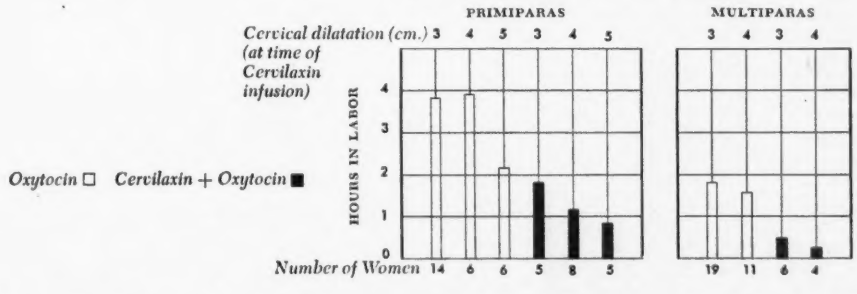
Q. How is Cervilaxin administered?

A. By intravenous drip.

Q. What is the dose?

A. Cervilaxin is supplied in 2 ml. vials containing 20 mg./ml. Usually this one dose is sufficient. Complete dosage and administration instructions are in the package literature.

Fig. 1. Time in labor—Oxytocin vs. Cervilaxin plus Oxytocin


PRIMIPARAS
MULTIPARAS
Cervical dilatation (cm.) (at time of Cervilaxin infusion)
3 4 5 3 4 5
3 4 3 4
HOURS IN LABOR
0 1 2 3 4
Oxytocin □ Cervilaxin + Oxytocin ■
Number of Women
14 6 6 5 8 5
19 11 6 4

1. Adapted from Birnberg, C. H. and Abitbol, M. M.: Refined Relaxin and Length of Labor, Obst. & Gynec., in press.
2. Eisenberg, L.: Facilitation of Full-Term Labor with Relaxin, in press.

Products of Original Research

NATIONAL

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Philadelphia 44, Pa.

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a new
direction
in
surface
anesthesia

Not a "caine" derivative. Good relief was provided in more than 15,600 case studies. Sensitization was negligible, and neither toxicity nor cross-sensitization was observed. Abbott

Safety First | in control of Nausea of Pregnancy

The first thought of every physician during the prenatal period is the safety of the patient.

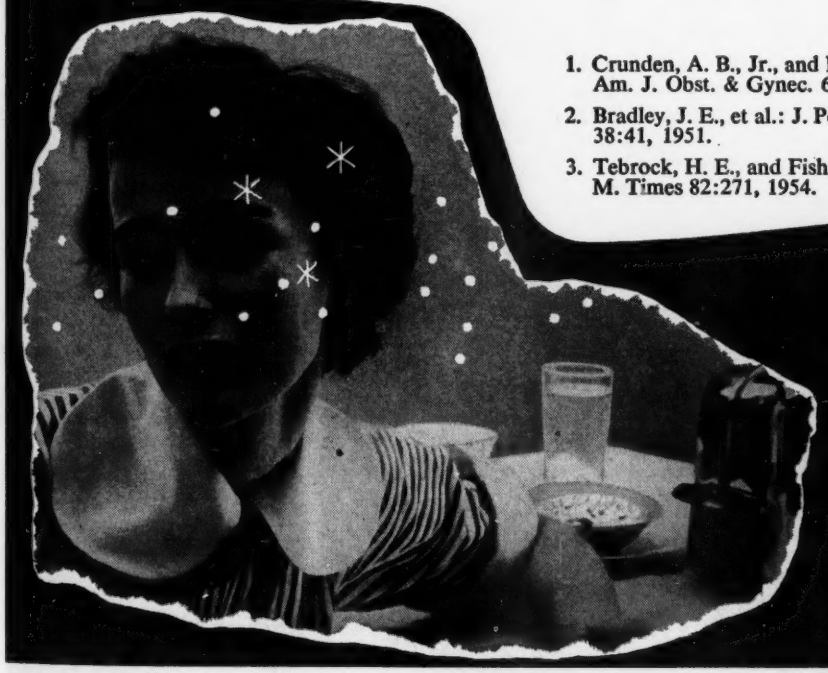
The first choice of the physician for an agent to control nausea and vomiting will be EMETROL® when he considers the following advantages:

1. EMETROL does not contain barbiturates, bromides, antihistamine compounds, or any other drugs likely to induce untoward effects.
2. EMETROL has been shown to be effective in nausea and vomiting in controlled clinical studies.[1-3]
3. EMETROL is so palatable that most patients will take it readily.
4. EMETROL works quickly, often bringing relief with the first dose.

SAFE

EMETROL®

(Phosphorated Carbohydrate Solution)



1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.
2. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.
3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

Kinney

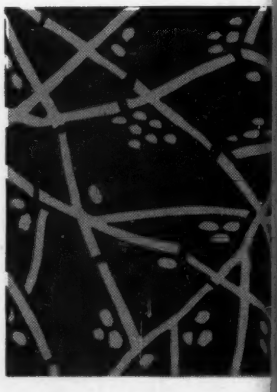
KINNEY & COMPANY, INC.
COLUMBUS, INDIANA

Presenting...an advance in

the treatment of **VAGINITIS**

TRICO

VAGINAL SUPPOSITORIES AND POWDE



a new specific moniliacide

MICOFUR[T. M.]

BRAND OF NIFUROXIME

now added to the established specific trichomonacide

FUROXONE®

BRAND OF FURAZOLIDONE

IMPROVED

FURON®

Rapid relief of burning and itching often within 24 hours

85.4% **CLINICAL CURES**† in 219 patients with either trichomonal vaginitis, monilial vaginitis, or both*, remissions were secured in 187.

71.4% **CULTURAL CURES**† 157 patients showed negative culture tests at 3 month follow-up examinations.

Eliminates malodor

Esthetically acceptable

Simple two-step treatment swiftly brings relief and control of vaginal moniliasis and trichomoniasis.

STEP 1 *Office* administration of TRICOFURON VAGINAL POWDER IMPROVED (Micofur 0.5% anti 5-nitro-2-furaldoxime and Furoxone 0.1% in an acidic water-soluble powder base) Applied by the physician at least once a week, except during menstruation.

For easy insufflation: plastic "puffer" bottle of 15 Gm., supplied with 3 sanitary disposable tips. Also available: glass bottle of 30 Gm.

STEP 2 Continued *home* use to maintain moniliacidal-trichomonacidal action: TRICOFURON VAGINAL SUPPOSITORIES IMPROVED (Micofur 0.375% and Furoxone 0.25% in a water-miscible base). Employed by the patient each morning and night the first week and each night thereafter—through one cycle, especially during the important menstrual days.

Box of 12, each hermetically sealed in green foil.

†Combined results of 12 clinical investigators. Data available on request.

*27% incidence of mixed Trichomonas and Candida (Monilia) albicans infection.

NITROFURANS . . . a *new* class of antimicrobials . . .
neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

Meat...

and the first trimester

The relationship between maintenance of nutritional well-being during the first three months of pregnancy and a lowered incidence of certain fetal abnormalities is now widely accepted. From a nutritional point of view the first trimester is no less important than the remainder of the gestational period.

Optimal nutritional status throughout gravidity is known to lessen some of the hazards of child-bearing and to diminish pediatric risk.

The nutritional demands of the first trimester are best met by an easily digested diet generous in protein, vitamins, and minerals, with a calorie allowance calculated not to exceed maternal and fetal requirements.

Generous amounts of meat in the daily diet help to fulfill these needs. Meat provides protein of high biologic quality. It is a valuable source of all known B vitamins, as well as the essential minerals iron, phosphorus, potassium, and magnesium. The easy and practically complete digestibility of meat and its reasonable caloric yield give it a preferred position in the diet recommended for the pregnant woman.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago . . . Members Throughout the United States

AN IMPORTANT ADVANCE IN MENOPAUSAL THERAPY

Because it replaces *half* control with *full* control.
Because it treats the *whole* menopausal syndrome.
Because *one* prescription manages *both* the psychic and somatic symptoms.

Two-dimensional treatment of the menopause

SUPPLIED: Bottles of 60 tablets.
Each tablet contains:

MILTOWN® (meprobamate, Wallace) ..... **400 mg.**
2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate.
U. S. Patent No. 2,724,720.

Conjugated Estrogens (equine) ..... **0.4 mg.**
Licensed under U. S. Patent No. 2,429,398.

DOSAGE: One tablet t.i.d. in 21-day courses with one week rest periods. Should be adjusted to individual requirements.

Samples and literature on request.

"Milprem"

MILTOWN®
A Proven Tranquilizer
+
CONJUGATED ESTROGENS (EQUINE)
A Proven Estrogen

WALLACE LABORATORIES, *New Brunswick, N. J.*
who discovered and introduced Miltown, the original meprobamate.

Psychic cycle

Anxiety, tension, and related symptoms exist in most gynecologic disturbances.

Symptoms of premenstrual tension (irritability, nervousness, headaches) were completely relieved with 'Miltown' in 78% of patients, and substantially relieved in all others studied.[1]

Patients with tension symptoms during menstruation became symptom-free on 'Miltown' therapy.[2]

'Miltown' *relaxes both mind and skeletal muscle* and alleviates somatic symptoms of anxiety, tension, and fear (usual dosage: 400 mg. q.i.d.). 'Miltown' therapy is notably safe, even in pregnancy,[3] and does not impair mental or physical efficiency.

References:

1. *Pennington, V. M.: Meprobamate (Miltown) in premenstrual tension. J.A.M.A.* **164**:*638, June 8, 1957.*
2. *Selling, L. S.: Clinical study of a new tranquilizing drug: use of Miltown (2-methyl-2-n-propyl-1,3-propanediol dicarbamate). J.A.M.A.* **157**:*1594, April 30, 1955.*
3. *Belafsky, H. A., Breslow, S. and Shangold, J. E.: Meprobamate in pregnancy. Obst. & Gynec.* **9**:*703, June 1957.*

Miltown®

THE ORIGINAL MEPROBAMATE
DISCOVERED & INTRODUCED BY
WALLACE LABORATORIES
NEW BRUNSWICK, NEW JERSEY

Johnson's

ANESTHETIC LUBRICATING JELLY

A sterile surgical lubricant possessing prompt local anesthetic properties. Non-irritating — water soluble.

Recommended for use in catheterization, endotracheal introduction, proctoscopy, cystoscopy and other similar uses.

Johnson & Johnson

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The many thousands of patients successfully treated with Signemycin* over the past year have confirmed the value of this safe and effective antibiotic agent. One further therapeutic resource is thereby provided the practicing physician who is faced daily in office and home practice with immediate diagnosis of common infections and the immediate institution of the most broadly effective therapy at his command, in his continuing task of the ever-extending control over human pathogens.

SIGNE

Now buffered to produce higher, faster blood levels; specify the V form on your prescriptions.

Supply: SIGNEMYCIN V Capsules, 250 mg. Signemycin Capsules, 250 mg. and 100 mg. Signemycin for Oral Suspension, 1.5 Gm., 125 mg. per 5 cc. teaspoonful, mint flavor. Signemycin Intravenous, 500 mg. vials and 250 mg. vials, buffered with ascorbic acid.

*TRADEMARK, OLEANDOMYCIN TETRACYCLINE
†TRADEMARK

Pfizer PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.
World leader in antibiotic development and production

"Eighty-seven patients with various infections of the skin were treated over a period of six weeks with [Signemycin]. Excellent or good results were achieved in sixty-seven, including eleven of twenty-two patients refractory to other antibiotics."

Lewis, H. H.; Frumess, G. M., and Henschel, E. J.: Rocky Mountain M. J. *54*:806 (Aug.) 1957.

"Results of treatment with oleandomycin-tetracycline of 50 infections [mostly respiratory] due to resistant organisms and 40 infections [respiratory, skin, urinary infections] due to sensitive organisms are very encouraging. In some of these patients, [Signemycin] was lifesaving, and in others surgery was made unnecessary. This confirms other reports."

Shubin, H.: Antibiotic Med. & Clin. Therapy *4*:174 (March) 1957.

Based on case reports documented by independent investigators in 26 countries abroad, the clinical response obtained with Signemycin in 1404 patients with a wide variety of infections was successful in 1329 patients; in 13 cases only was it necessary to discontinue therapy because of side effects.

Report on 1404 Cases Treated with Signemycin: Medical Department, Pfizer International. Available on request.

In 50 nonselected patients, Signemycin ". . . appears to be effective in the treatment of most general surgical infections, including virulent staphylococcus aureus infections. In some cases these infections had been clinically resistant to other antibiotics. The drug is apparently well tolerated."

Levi, W. M., and Kredel, F. E.: J. South Carolina M. A. *53*:178 (May) 1957.

Of 50 patients with various infectious processes, 26 had not responded to previous antibiotic therapy. With Signemycin "Ninety-six per cent of the mixed infections were clinically controlled. . . . and in none of the cases was there any reason to discontinue the drug."

Winton, S. S., and Chesrow, E.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 55.

Signemycin in 79 patients with severe soft tissue infections: "The average response of these cases was excellent and inflammatory symptoms subsided with almost uniform rapidity. . . . The magnitude and incidence of surgical intervention was reduced. . . . Side reactions were minimal. . . ."

LaCaille, R. A., and Prigot, A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 67.

Five groups of patients (total 211) with acne were treated with one of five antibiotic agents, including Signemycin (55 cases). "The results were evaluated taking into consideration the usual response to such conservative conventional therapy and the rapidity of response." During a period of 8 weeks, Signemycin rapidly attained and maintained the highest percentage of efficacy of antibiotic agents tried.

Frank, L., and Stritzler, C.: Antibiotic Med. & Clin. Therapy *4*:419 (July) 1957.

In the treatment of 78 patients with tropical infections, some complicated by multiple bacterial contamination or present for years, Signemycin was found to be ". . . an exceptionally effective agent," requiring smaller doses and less extended periods of therapy than with the tetracyclines alone, and "caused no notable toxic reactions."

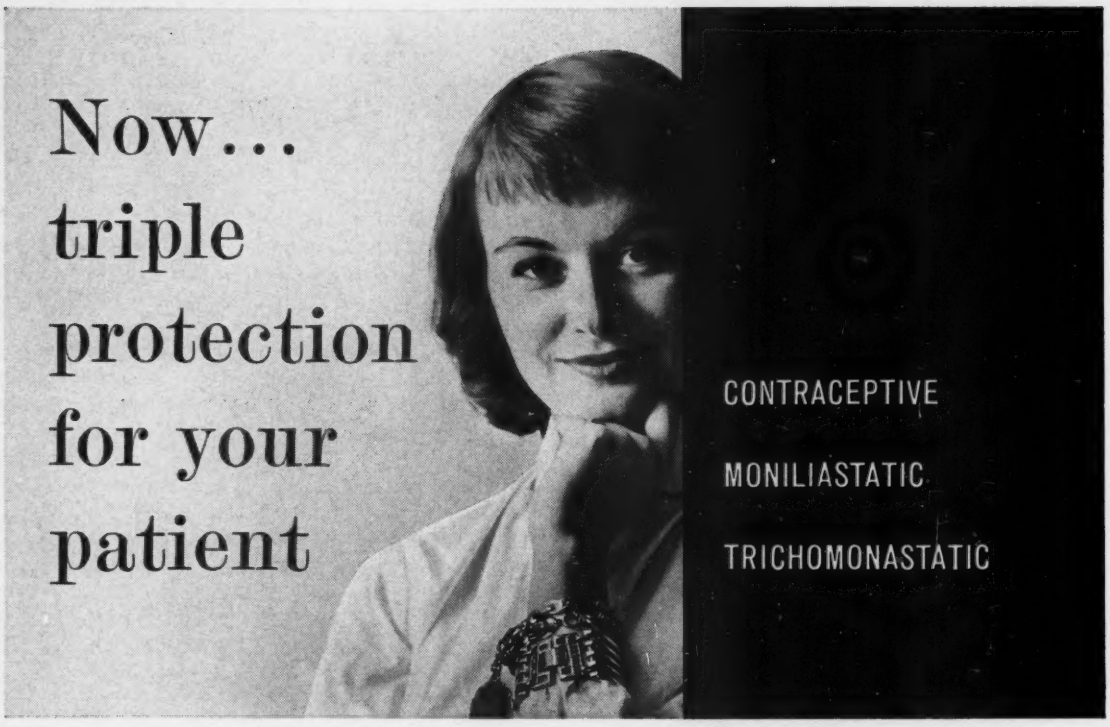
Loughlin, E. H., and Mullin, W. G.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 63.

MYCIN† V

OLEANDOMYCIN TETRACYCLINE-PHOSPHATE BUFFERED

PROVED CLINICALLY EFFECTIVE

When specifying buffered Signemycin V be sure to write the *V* on your Rx



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LANTEEN contraceptive jelly enables all your patients to use continuously the safest conception control method. Even your problem patients do not have to interrupt the diaphragm-jelly technique. The evident increase in the incidence of moniliasis suggests the use of a contraceptive that has been shown in the laboratory to be moniliastatic. Also, LANTEEN jelly's proven activity against trichomonas can aid in preventing reinfection with this organism by the male partner.

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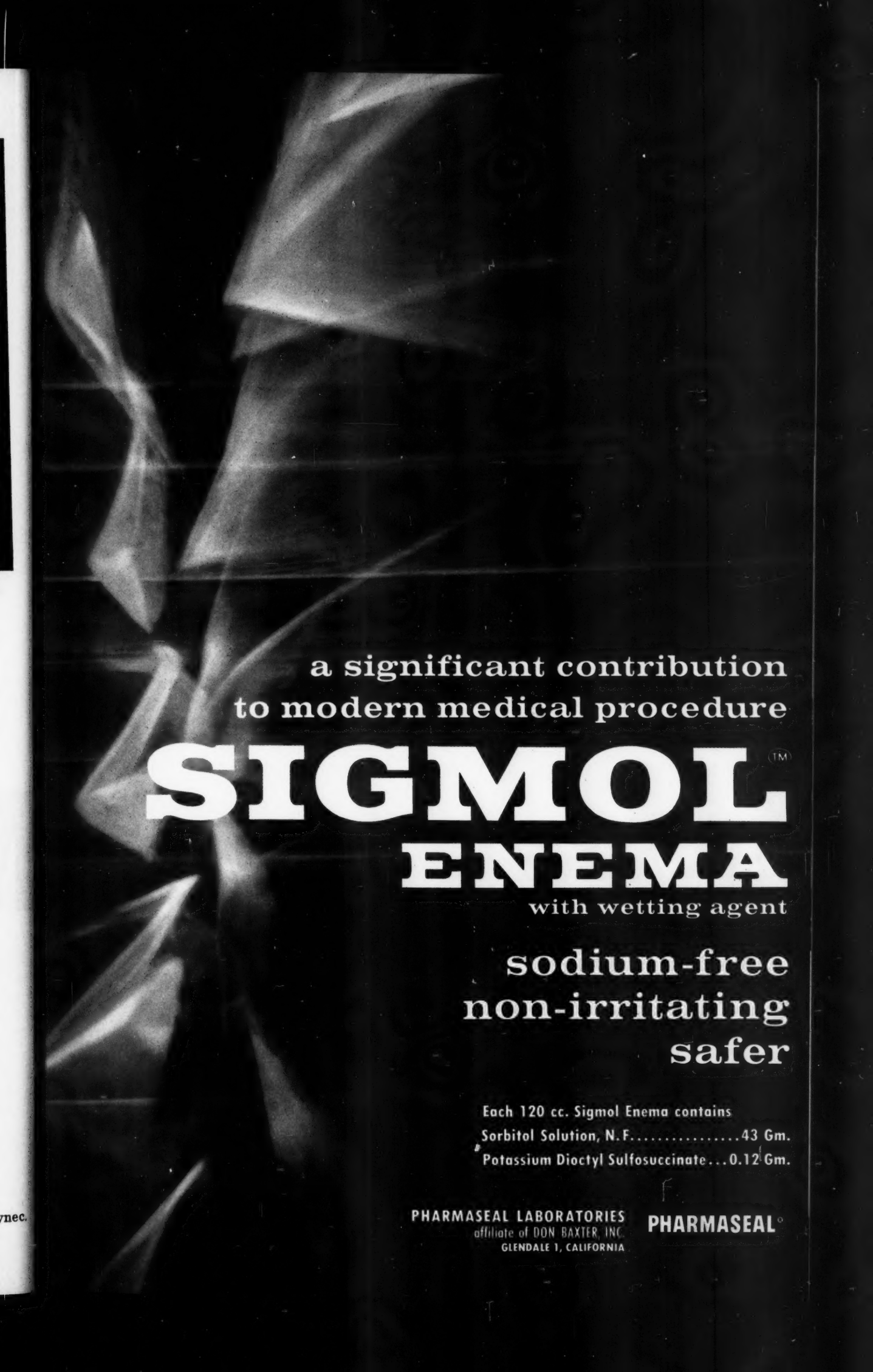
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ENEMA
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Each 120 cc. Sigmol Enema contains
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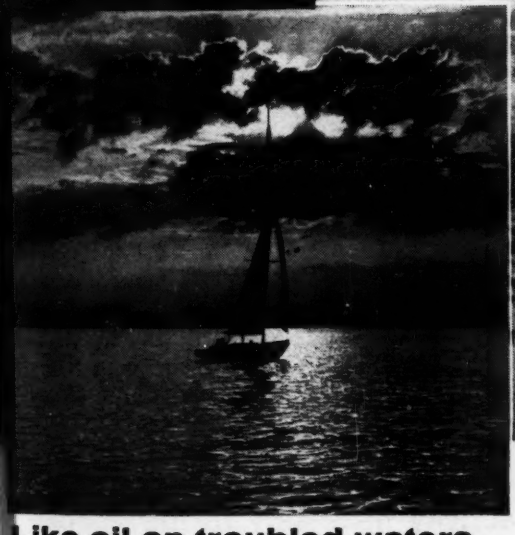
When smooth muscle spasm gets rough on your patients



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through provision of natural belladonna alkaloids in optimal ratio, with phenobarbital

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DONNATAL ELIXIR (per 5 cc.)

Hyoscyamine Sulfate	0.1037 mg.
Atropine Sulfate	0.0194 mg.
Hyoscine Hydrobromide	0.0065 mg.
Phenobarbital (¼ gr.)	16.2 mg.

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RESEARCH ANNOUNCES

ENOVID*

BRAND OF NORETHYNODREL WITH ETHYNYLESTRADIOL 3-METHYL ETHER

new oral synthetic endometropin for control of menstrual irregularities

Enovid contains norethynodrel, a new synthetic endometropic steroid with strong progestational and slight estrogenic activity. The estrogenic activity is enhanced by ethynylestradiol 3-methyl ether.

Enovid simulates the normal ovarian activity necessary to the maintenance of regular menstrual cycles.

Acting on the endometrium, the vaginal mucosa and the anterior pituitary, Enovid therapy has proved effective in the regulative control of such irregularities as primary and secondary amenorrhea[1-3], dysmenorrhea[4], prolonged or excessive menstrual bleeding[1,5] and distressing premenstrual tension[5].

INDICATIONS AND DOSAGE GUIDE FOR ENOVID

CONDITIONS	FIRST CYCLE	SECOND AND THIRD SUCCEEDING CYCLES
Amenorrhea (Primary or Secondary)	One tablet daily for 20 days to establish cycle	One tablet daily from day 5 to day 25*
Metrorrhagia	One or two tablets daily to day 25 or for 10 days to establish cycle†	Same as above
Menorrhagia	One or two tablets daily through balance of cycle†	Same as above
Oligomenorrhea	One tablet daily from day 5 to day 25*	Same as above
Dysmenorrhea	One tablet daily from day 5 to day 25‡	Same as above
Premenstrual Tension	One tablet daily from day 15 to day 25§	Same as for first cycle
Inadequate Luteal Phase	One tablet daily from day 15 to day 25	Same as for first cycle

*The administration of Enovid prior to day 15 may interfere with ovulation and if this is undesired, day 15 to day 25 may be substituted.

†If the patient is bleeding when first seen, two tablets will usually control the bleeding. In some patients less severe bleeding may be controlled with one tablet. The dosage used should be continued through the remainder of the cycle.

‡If dysmenorrhea is due to endometriosis, a special dosage schedule is required; Kistner[6] suggests 10 mg. daily for two weeks, 20 mg. daily for two weeks, 30 mg. daily for two weeks and 40 mg. daily for two to five months.

§Heller[5] recommends one tablet every twelve hours from day 5 to day 25 for two or three cycles.

REFERENCES:

1. Southam, A. L.; 2. Roland, M.; 3. Kupperman, H. S., and Epstein, J. A.; 4. Weinberg, C. H.: Papers Presented during a Symposium on Steroid Compounds Exhibiting Progestational Effects, Chicago, Searle Research Laboratories, January 23, 1957, to be published. 5. Heller, C. G.: Internat. Rec. Med. 169:760 (November) 1956. 6. Kistner, R. W.: The Use of Newer Progestins in the Treatment of Endometriosis—A Pseudopregnancy, Section on Obstetrics and Gynecology, American Medical Association, New York, June 5, 1957.

FORMULA:

Each 10-mg. tablet of Enovid contains norethynodrel, a new synthetic steroid, and 0.15 of ethynylestradiol 3-methyl ether.

*TRADEMARK OF G. D. SEARLE & CO.

Supplied in uncoated, scored, coral-colored tablets.

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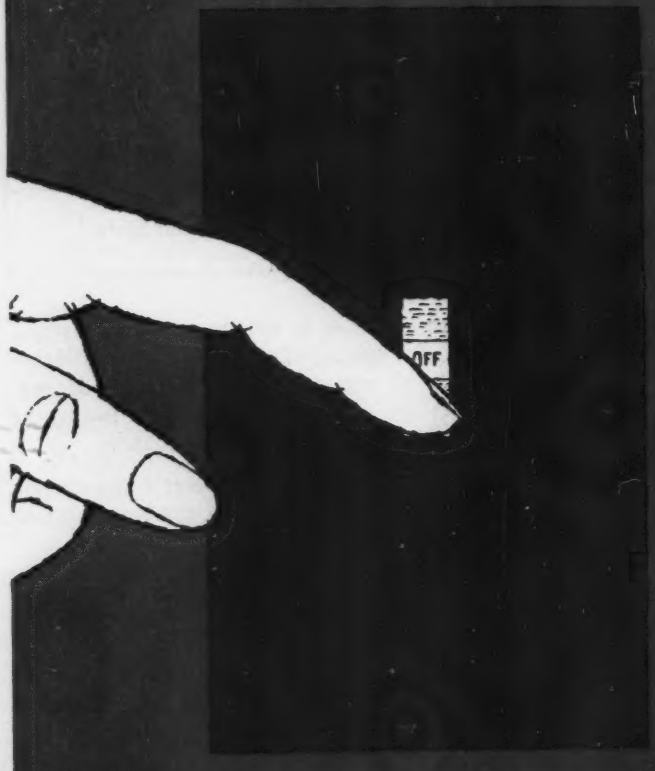
YOU CAN TURN OFF THE COUGH UNTIL MORNING...

TUSSIONEX™

A 'Strasionic' Release Product • Dihydrocodeinone Resin—Phenyltoloxamine Resin



A SINGLE DOSE GIVES 8-12 HOUR CONTROL

through sustained 'Strasionic' release.

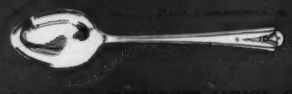
Suppresses nighttime sleep-robbing, daytime distracting, useless coughs without interfering with the protective cough mechanism.

Over 12,000 clinical observations[1, 2, 3, 4] demonstrate its wide field of usefulness in ages ranging from 3 months to more than 70 years.

REFERENCES

(1) Chan, Y. T. and Hays, E. E. The American Journal of the Medical Sciences, August 1957; (2) Townsend, E. H., Jr., In Press; (3) Weismiller, F., In Press; (4) Cass, Leo J. and Frederik, W. S., In Press.

Now Available on Your Prescription



EACH TUSSIONEX TABLET CONTAINS:
5 mg. Dihydrocodeinone as a resin complex
10 mg. Phenyltoloxamine as a resin complex
Stock bottle of 100

EACH TEASPOON (5cc) TUSSIONEX LIQUID CONTAINS:
5 mg. Dihydrocodeinone as a resin complex
10 mg. Phenyltoloxamine as a resin complex
Stock bottle of 16 oz.

SUGGESTED DOSE: One tablet or teaspoon (5cc) q12h. Rx only. Class B taxable narcotic.

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Originators of 'Strasionic' (sustained ionic) release

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An established systemic hemostat

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SALICYLATE*

(Brand of carbazochrome salicylate)

effective in virtually every operative procedure

The reports of numerous investigators have established the effectiveness of Adrenosem Salicylate in the control of bleeding. It has been used prophylactically and therapeutically in virtually every operative procedure. Following are some of the procedures and conditions where its usefulness has been demonstrated:

Tonsillectomy, adenoidectomy and nasopharynx surgery
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Hematuria
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Pulmonary bleeding
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One of the many uses of **Adrenosem®**
SALICYLATE

Adrenosem Salicylate is useful in every operative procedure where bleeding and oozing are problems. This hemostatic agent controls blood loss by maintaining normal capillary permeability and by promoting the retraction of severed capillary ends.

One clinician states: "At the recommended dosage levels there are no contraindications. Patients treated for more than two years show no toxic effects attributable to the drug."[1]

Adrenosem Salicylate is supplied in

Ampuls
Tablets
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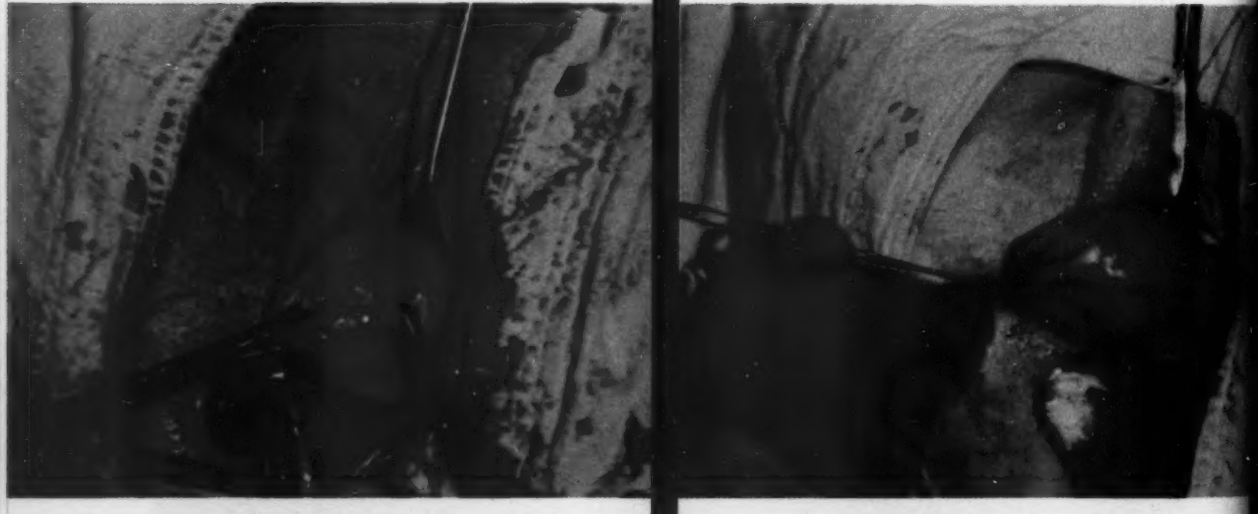
1. Riddle, A.C., Jr.: Adrenosem Salicylate: A Systemic Hemostat, Oral Surg., Oral Med., Oral Path. 6:617 (June, 1955).



Vaginal hysterectomy.
Without Adrenosem. Note bloody field.

Vaginal hysterectomy.
With Adrenosem. Note dry field.

Write for comprehensive illustrated brochure describing the action and uses of Adrenosem Salicylate.

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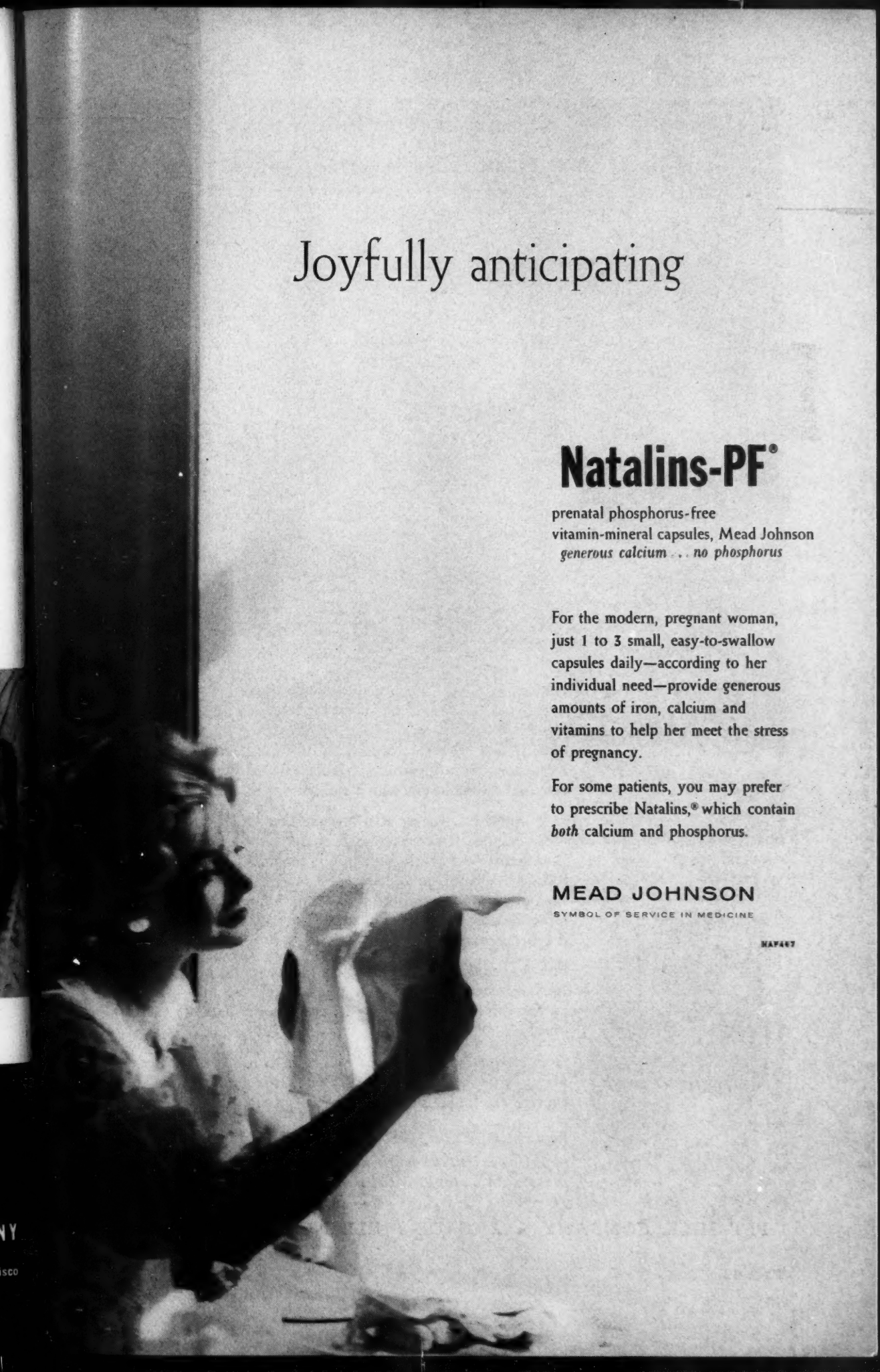
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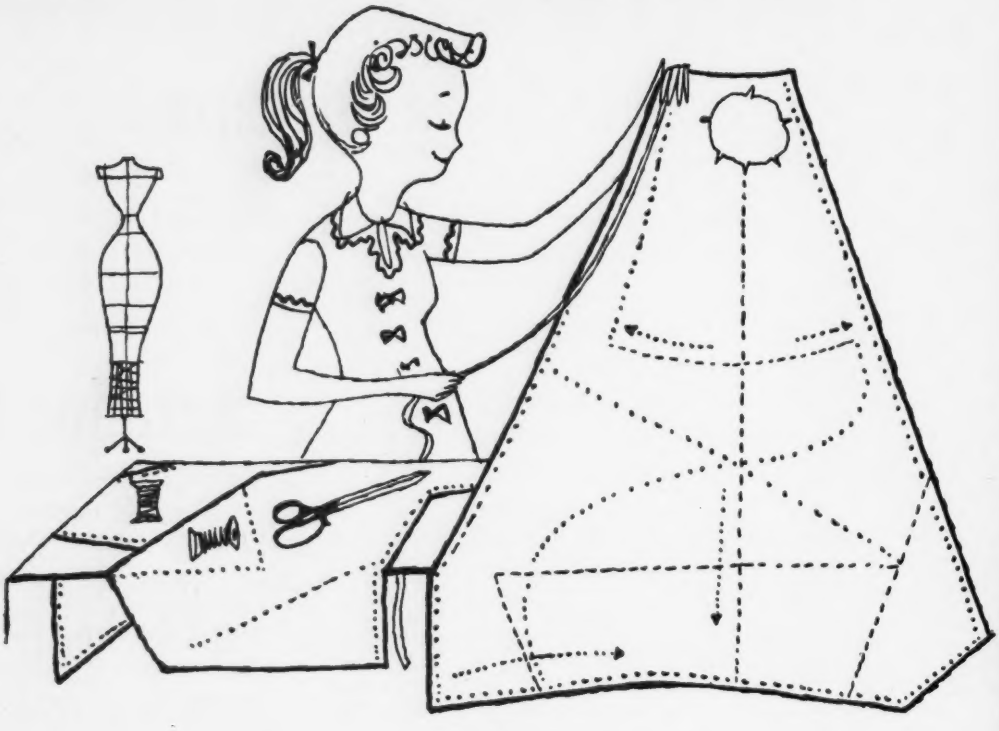
when nourishment must adjust to this changing pattern . . .



Fortunate, but rare, is the expectant mother whose established diet pattern fits the particular needs of pregnancy. More frequently, her physician discovers that the *quality* of her diet requires some adjustment, particularly with respect to the essential nourishment which milk supplies.

In such cases, *Instant* Pet Nonfat Dry Milk can often be most helpful. It provides high-quality protein, calcium, and B-vitamins—all of the best things in milk—in concentrated form, which can be added to prepared dishes without substantially increasing calories. By using *Instant* Pet in dry form, milk nourishment can be included in many foods where milk is not normally used.

For the mother whose problem is too-rapid weight gain, *Instant* Pet, reconstituted, supplies a delicious milk-without-fat for drinking or cooking . . . with only half the calories of whole milk.

And *Instant* Pet, a valuable addition to the diet of the expectant mother, is also a thrifty one. It is generally available everywhere for as little as 8 cents a quart.

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supplies essential milk nourishment with minimum caloric intake at minimum cost

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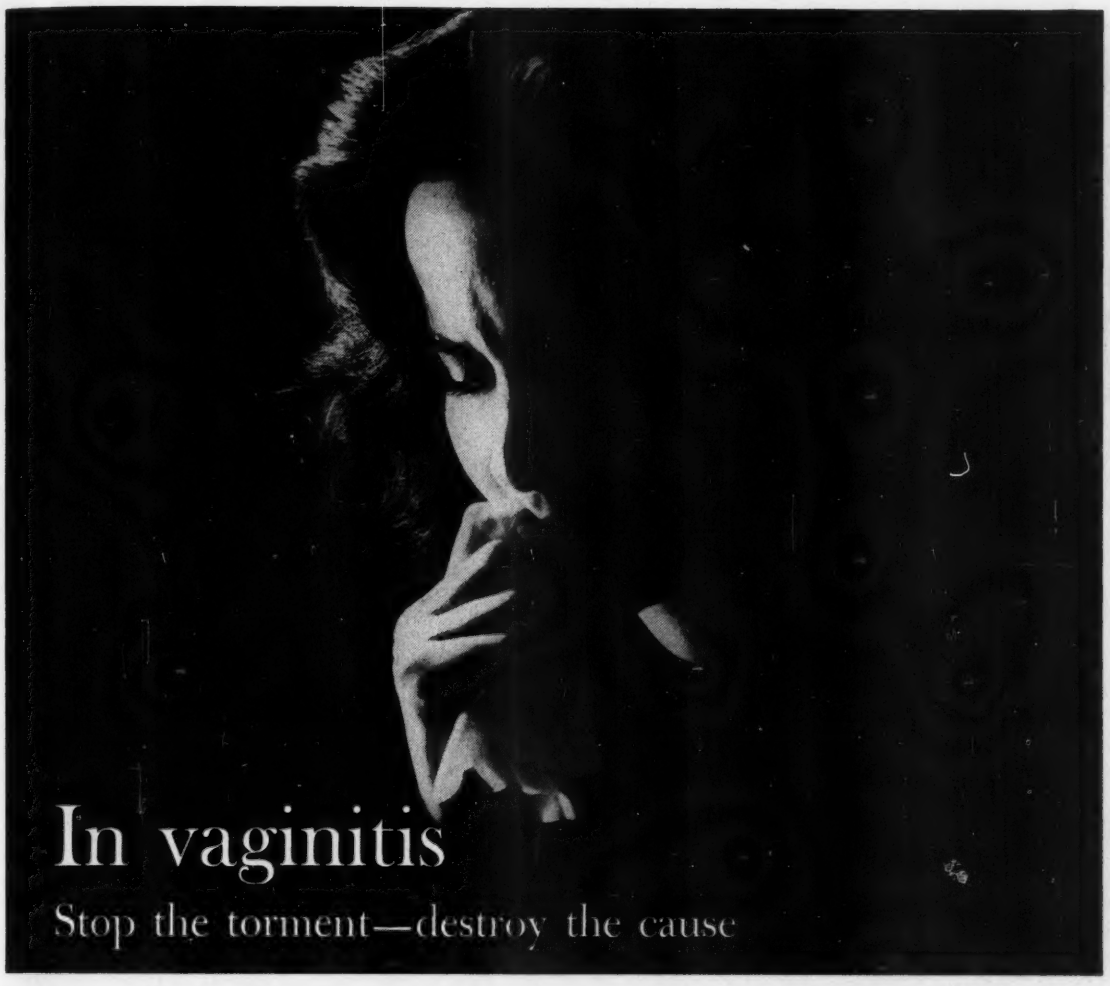

AVC

Improved

in trichomonal vaginitis –
"... the most effective treatment available."[1]

in monilial vaginitis –
"... more effective than any other agent ... used previously."[2]

in mixed infection –
"... the most effective treatment of endocervicitis. ..."[3]

The rate of cure with AVC Improved is consistently high in all common types of vaginitis. In one series of patients with trichomonal vaginitis, bacteriologic cures were obtained in 82.5% of the cases.[1] Symptomatic relief is rapid and lasting. And because AVC Improved has an acid pH, it encourages the early return of normal vaginal flora.

Composition: A nonstaining cream containing 9-aminoacridine hydrochloride 0.2%; sulfanilamide 15.0%; allantoin 2.0%; with lactose in a water-miscible base buffered to pH 4.5.

Indications: Trichomonal leukorrhea; monilial and nonspecific vaginitis; cervicitis; postpartum hygiene; pre- and postcauterization, coagulation, conization, and other vaginal surgery; vaginal infections in children.

Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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NEW better tolerated source of iron–ferrous fumarate–helps eliminate gastric upset. **NEW** non-inhibitory intrinsic factor assures greater B_{12} absorption to meet increased requirements. **NEW** more comprehensive formulation includes phosphorus-free calcium, Vitamins K and B_6, plus important minerals and trace elements. **NEW** Reminder Jar... she'll keep it handy on the dining table... use it later for diaper pins or cotton. Your patients pay no more for the added benefits of FILIBON.

Each capsule contains:

Vitamin A	4,000 U.S.P. Units	Iron (as Fumarate)	30 mg.
Vitamin D	400 U.S.P. Units	Fluorine (as CaF_2)	0.015 mg.
Thiamine Mononitrate (B_1)	3 mg.	Intrinsic Factor	5 mg.
Pyridoxine (B_6)	1 mg.	Copper (as CuO)	0.15 mg.
Niacinamide	10 mg.	Iodine (as KI)	0.01 mg.
Riboflavin (B_2)	2 mg.	Potassium (as K_2SO_4)	0.835 mg.
Vitamin B_{12}	2 mcgm.	Manganese (as MnO_2)	0.05 mg.
Ascorbic Acid (C)	50 mg.	Magnesium (as MgO)	0.15 mg.
Vitamin K (Menadione)	0.5 mg.	Molybdenum (as $Na_2MoO_4 \cdot 2H_2O$)	0.025 mg.
Folic Acid	1 mg.	Zinc (as ZnO)	0.085 mg.
Ferrous Fumarate	90 mg.	Calcium Carbonate	575 mg.

Dosage: One or more capsules daily. **Supplied: Attractive, re-usable bottles of 100 capsules.**

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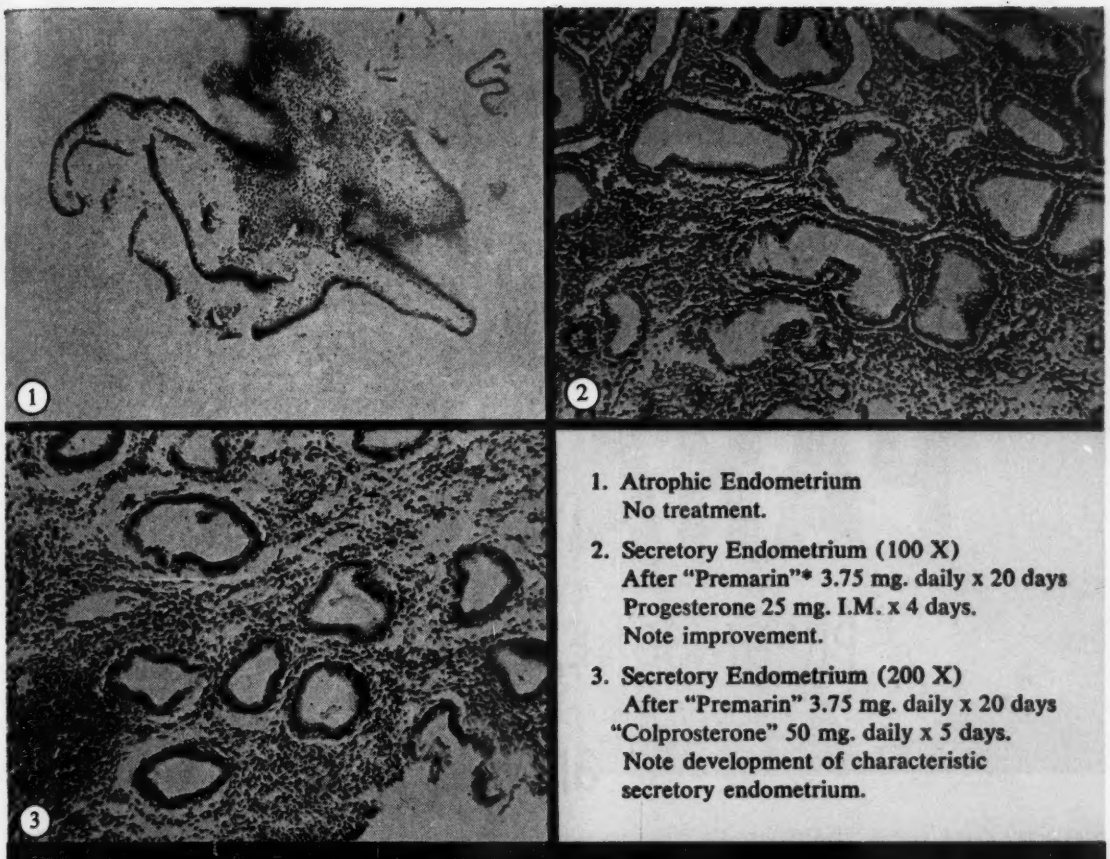

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   After "Premarin"* 3.75 mg. daily x 20 days
   Progesterone 25 mg. I.M. x 4 days.
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The only dosage form of progesterone combining convenience of administration with a high degree of effectiveness for greater patient acceptability.

"Colprosterone" therapy provides:

- freedom from pain and inconvenience of injection
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Literature with complete dosage regimens for *amenorrhea, habitual abortion, premenstrual tension* and other indications available on request.

Supplied: No. 793 – 25 mg. vaginal tablets (silver foil), No. 794 – 50 mg. vaginal tablets (gold foil), boxes of 30. Combination package – 15 vaginal tablets with applicator.

Each tablet is individually and hermetically sealed. Presented in strips of 3 units, detachable as required.

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"FURADANTIN possesses such desirable characteristics as stability, a wide antibacterial spectrum, and little tendency to permit development of bacterial resistance; considerations which are particularly important when treating the pregnant patient."[1]

A recent report by Nesbitt and Young[1] emphasizes the unique value of FURADANTIN *in the treatment of urinary tract infections associated with pregnancy. The following highlights from this paper impressively document* FURADANTIN'S *effectiveness and safety:*

THE CLINICAL SAMPLE: "A total of 104 women with bacterial infections of the urinary tract were treated with FURADANTIN during pregnancy and the puerperium . . . The clinical diagnoses included chronic or recurrent cystitis and pyelonephritis."

CLINICAL AND BACTERIOLOGIC RESULTS: "FURADANTIN was highly effective in the treatment of these infections during all stages of pregnancy and the postpartum period. . . . Of the 42 patients treated with 100 mg. FURADANTIN q.i.d., 27 (69 per cent) were cured bacteriologically and clinically; the remaining 15 became asymptomatic but continued to harbor the pathogens as shown by culture. There were no clinical failures in this group. In most patients the beneficial effect of treatment was obvious within the few few days."

SIDE EFFECTS: "Side effects of FURADANTIN therapy were noted in only 17 patients and were mostly quite mild and inconsequential. . . . The obstetric course was satisfactory in all, and there was no evidence that the fetus was in any way affected by the therapy."

CONCLUSIONS: "FURADANTIN, in doses up to 100 mg. q.i.d. for a period of 7 days, is an effective and safe antibacterial chemotherapeutic agent for urinary tract infections. Pregnancy does not contraindicate its use."

FURADANTIN *effective and safe in pregnancy* [1,2,3]

AVERAGE FURADANTIN DOSAGE IN PREGNANCY: Acute complicated, refractory or chronic urinary tract infections—100 mg. q.i.d. Acute uncomplicated urinary tract infections—50 mg. q.i.d. (If patient unresponsive after 2 or 3 days, increase dose to 100 mg. q.i.d.)

ADMINISTRATION: With meals and with food or milk on retiring. Continue for 3 days after urine becomes sterile.

SUPPLIED: Tablets, 50 and 100 mg., bottles of 25 and 100.
Oral Suspension, 25 mg. per 5 cc. tsp., bottle of 60 cc.
(Readily miscible with water, milk or fruit juices.)

REFERENCES: 1. Nesbitt, R. E. L., Jr., and Young, J. E.: Obst. Gyn., N. Y. 10:89, 1957. 2. Diggs, E. S.; Prevost, E. C., and Valderas, J. G.: Am. J. Obst. 71:399, 1956. 3. MacLeod, P. F.; Rogers, G. S., and Anslowar, B. R.: Internat. Rec. Med. 169:561, 1956.

NOW, for hospitalized patients, for severe urinary tract infections when peroral administration of FURADANTIN is not feasible and for serious infections as septicemia (bacteremia) when the bacterium is sensitive:
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NITROFURANS . . . a *new* class of antimicrobials . . .
neither antibiotics nor sulfonamides

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"Really?"

Yes . . .

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to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR

recommended for routine prophylaxis in ALL pregnancies . .

96 per cent live delivery with **des**PLEX in one series of 1200 patients[4]—
— bigger and stronger babies, too.[cf. 1]

No gastric or other side effects with **des**PLEX
— in either high or low dosage[3,4,5]

(Each **des**PLEX tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating *to assure prompt help in emergencies.* **des**PLEX tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

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REFERENCES

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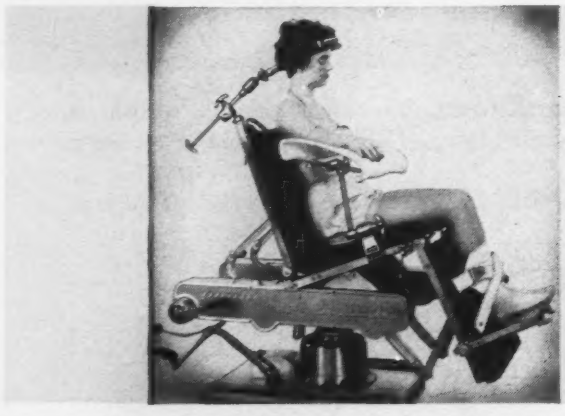

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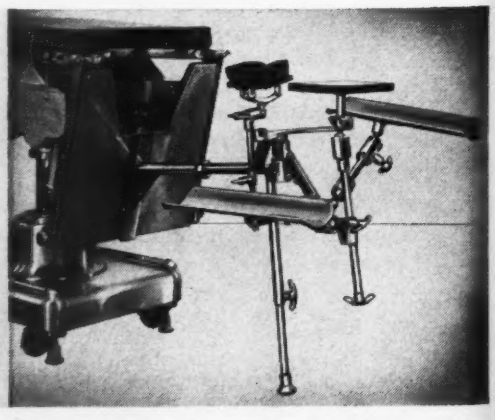

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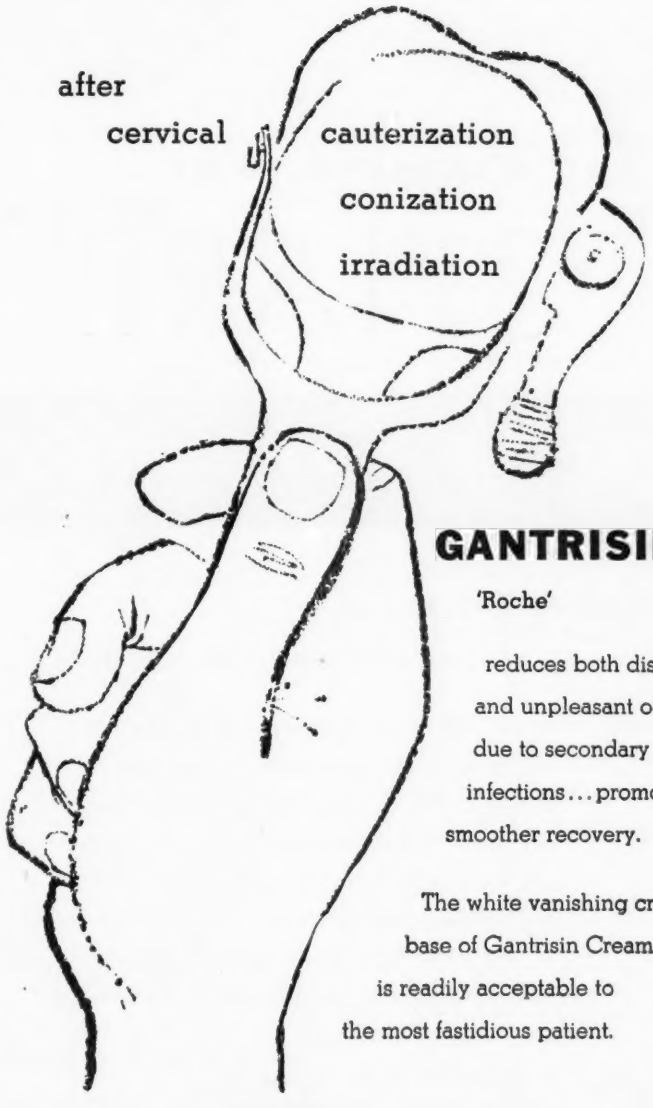

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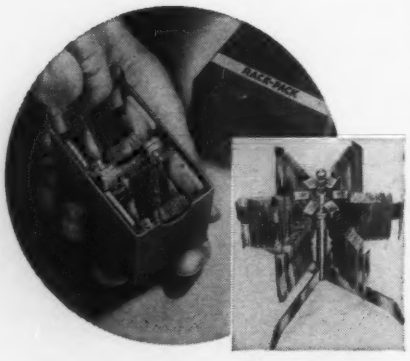

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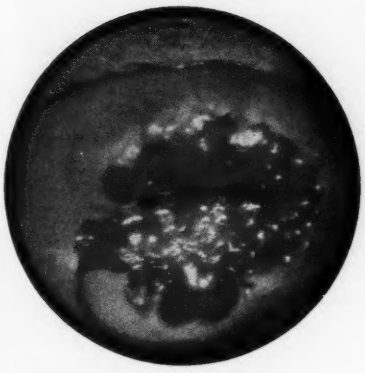

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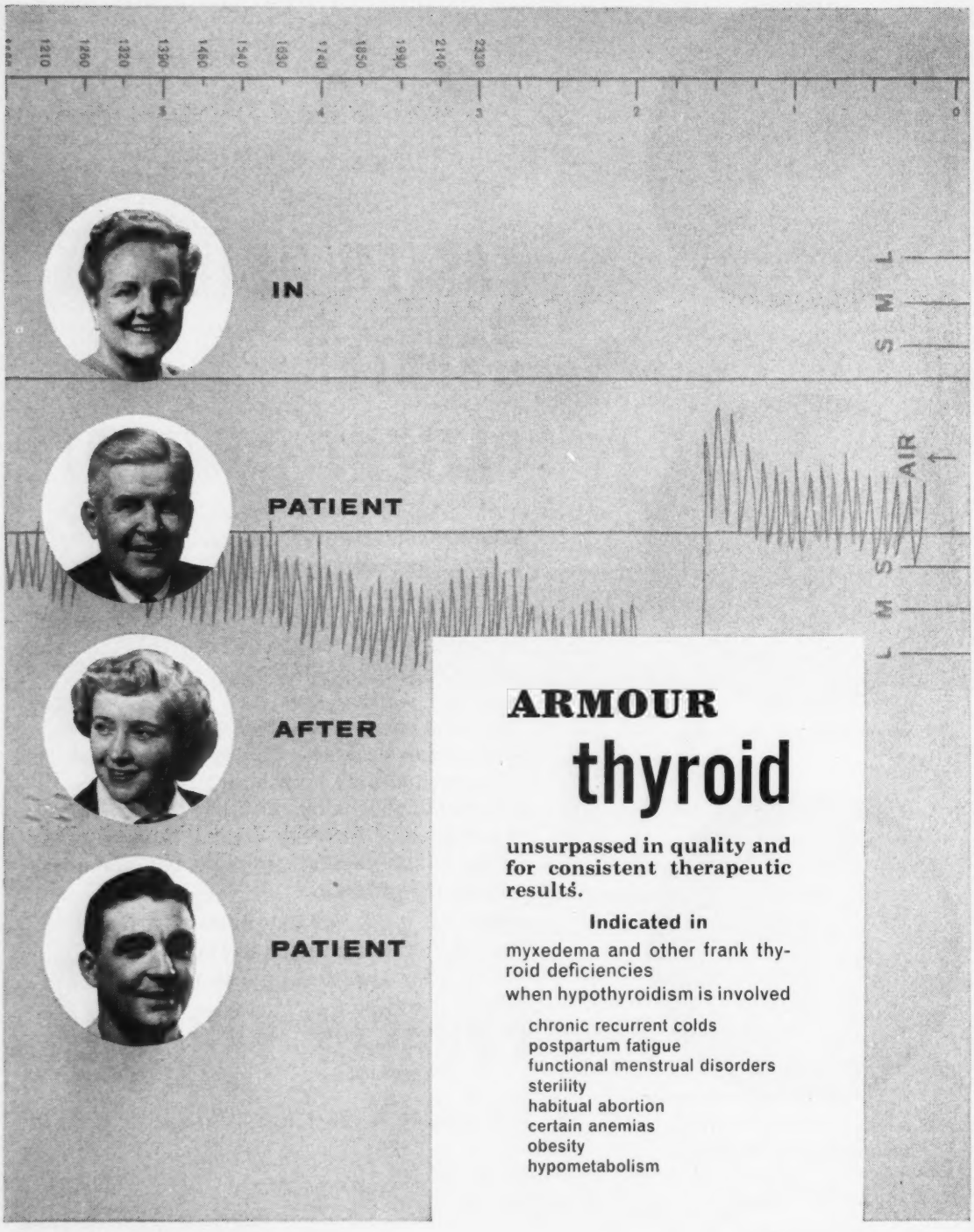

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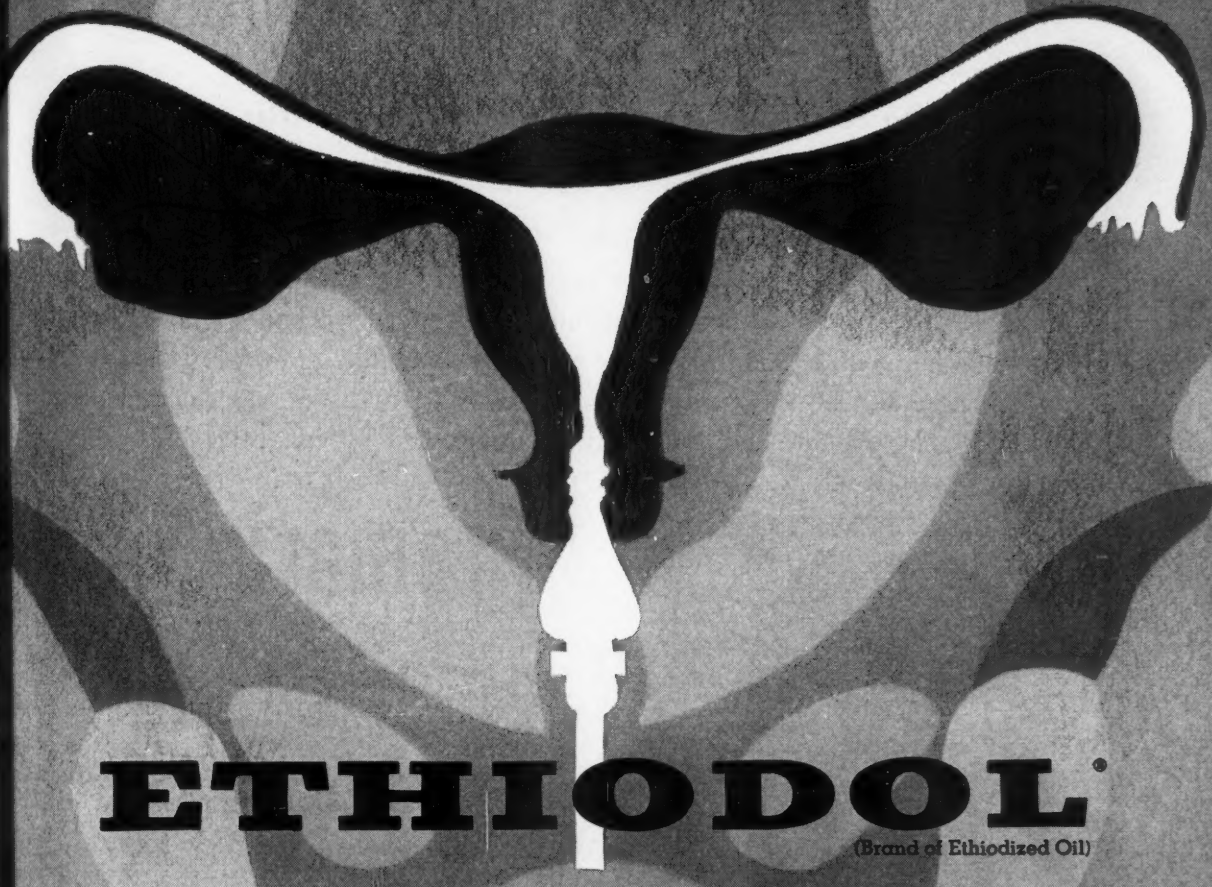

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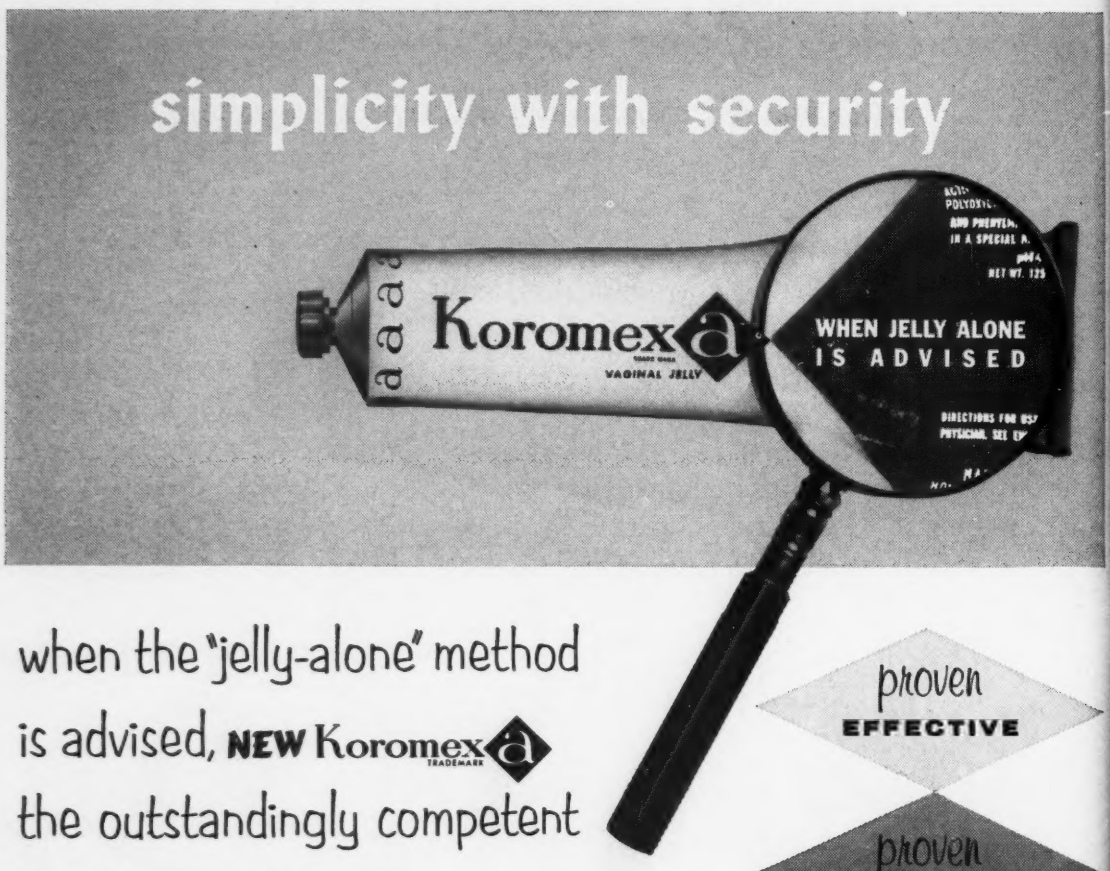

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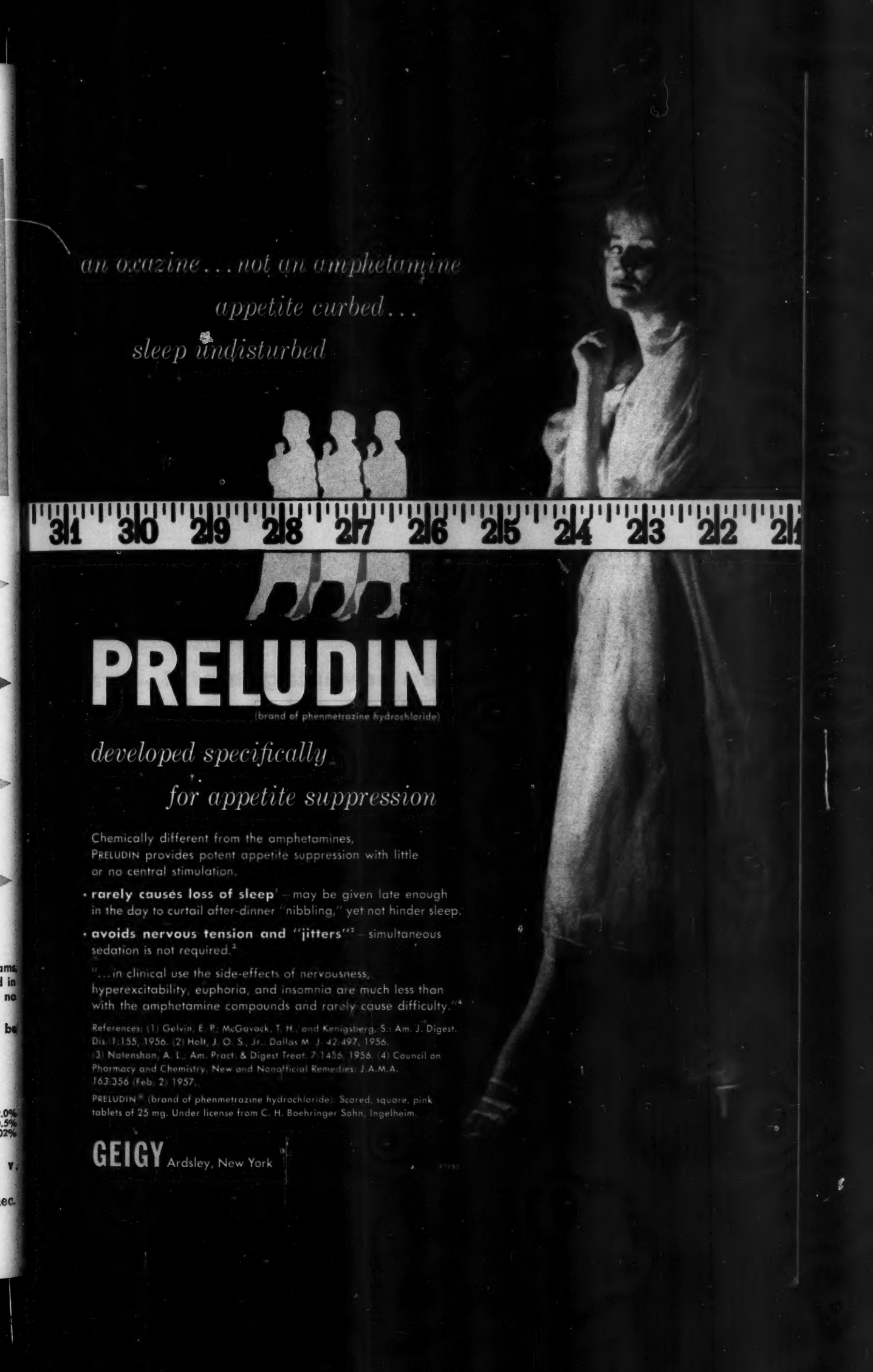
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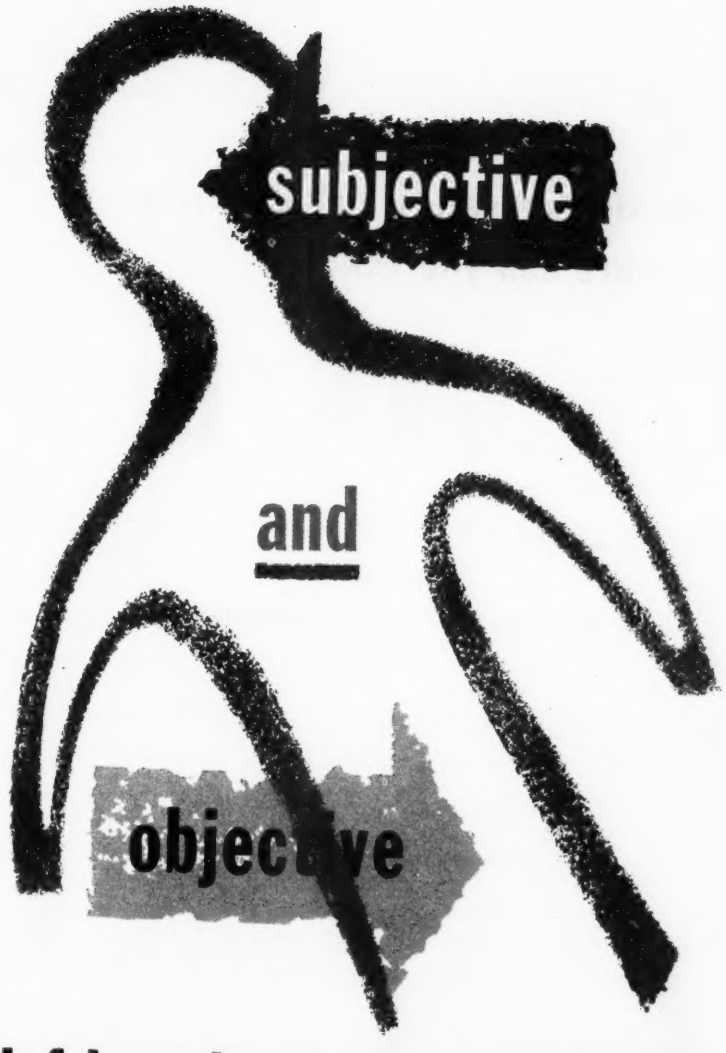

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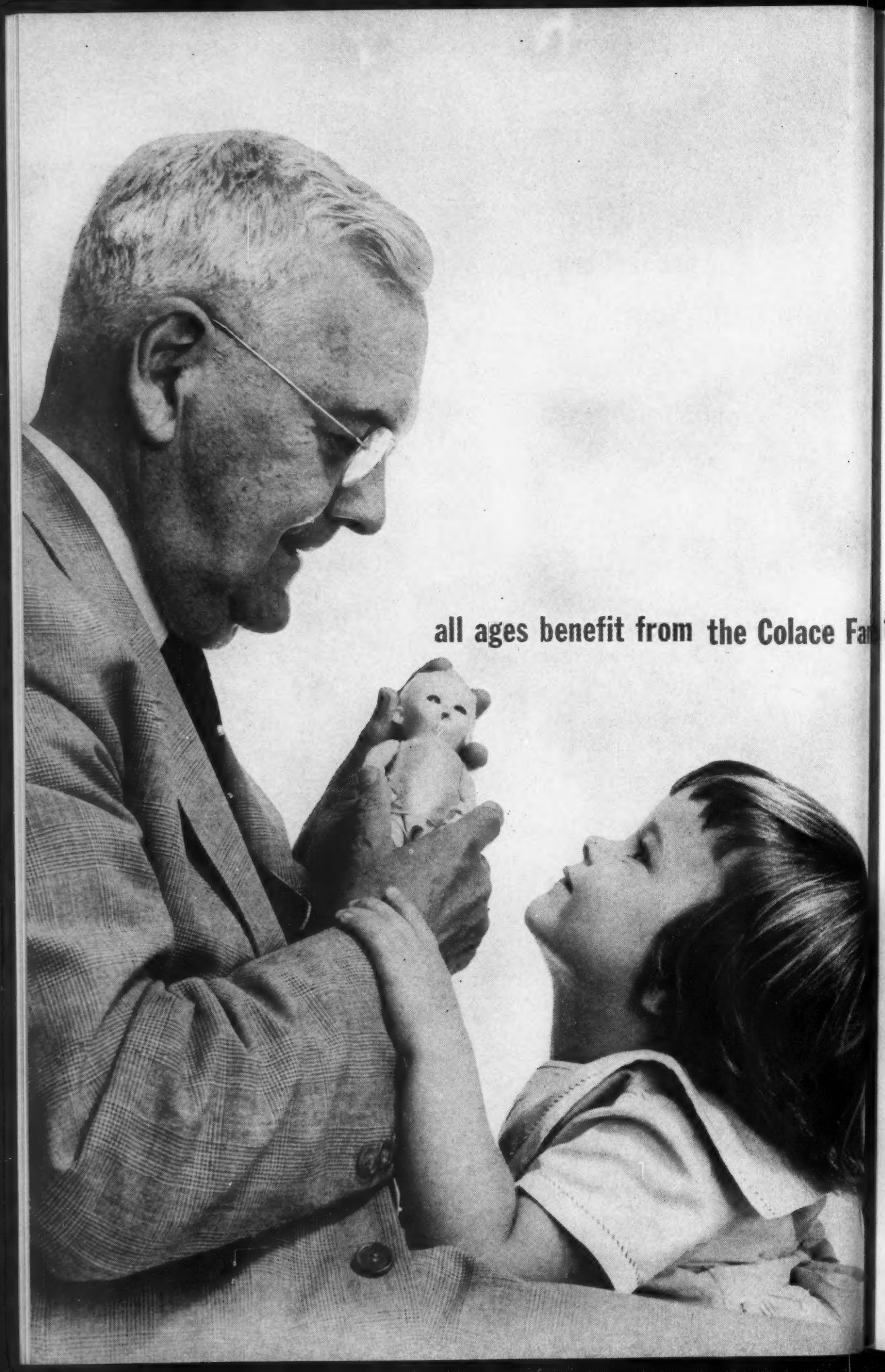
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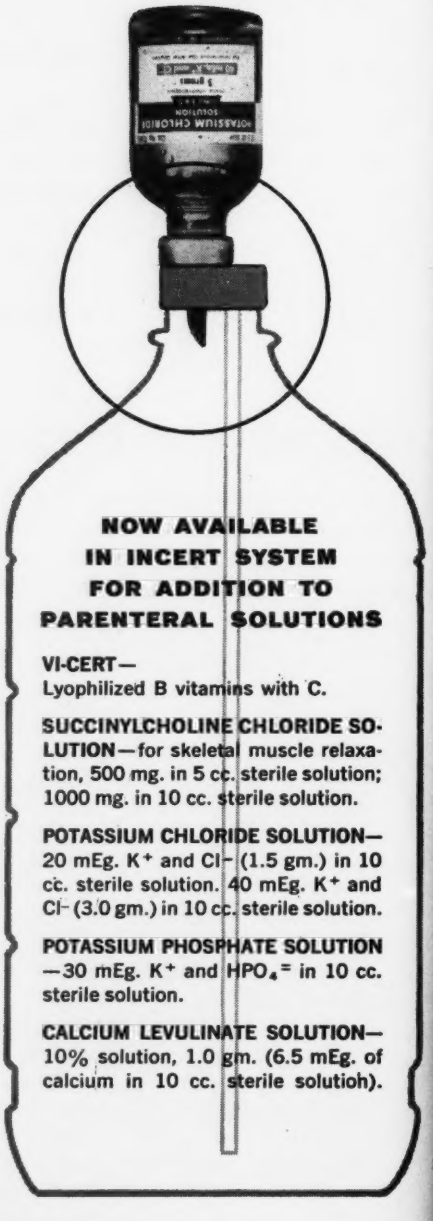

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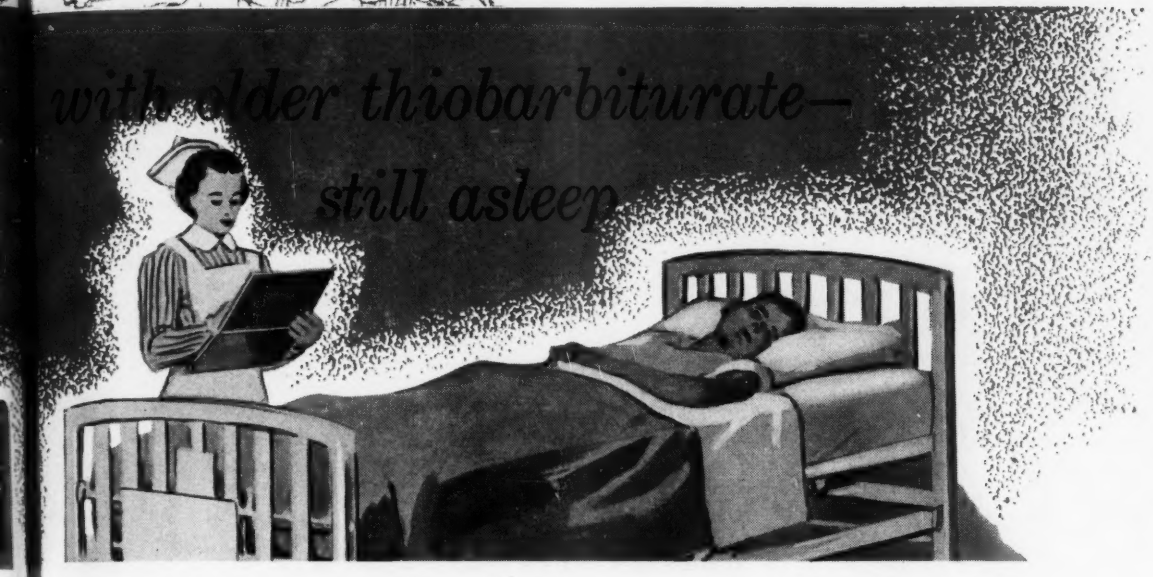

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(1) Boone, J. D.; Muñoz, R., and Dillon, J. B.: Anesthesiology *17*:284, 1956. (2) Zima, O.; von Werder, F., and Hotovy, R.: Anaesthesist *3*:244, 1954. (3) Mersch, M. A.; Clarie, D'A., and Fitzpatrick, L. J.: J.M. Soc. New Jersey *53*:414, 1956. (4) Blake, M. W., and Perlman, P. L.: J. Pharmacol. & Exper. Therap. *117*:287, 1956. (5) Irwin, S.; Stagg, R. D., Dunbar, E., and Govier, W. M.: J. Pharmacol. & Exper. Therap. *116*:317, 1956. (6) Ayd, F. J., Jr.: Neraval: A new anesthetic for electroconvulsive therapy, Paper presented at annual meet., Electroshock Research Association, Chicago, Illinois, April 29, 1956. (7) Reifferscheid, M., and Dietmann, K.: Deutsche med. Wchnschr. *79*:638, 1954. (8) Houde, J., Hudon, F., and Jacques, A.: Neraval (methitural sodium), Paper presented at Meet., Canad. Anaesth. Soc., Quebec City, P. Q., May 5, 1956.

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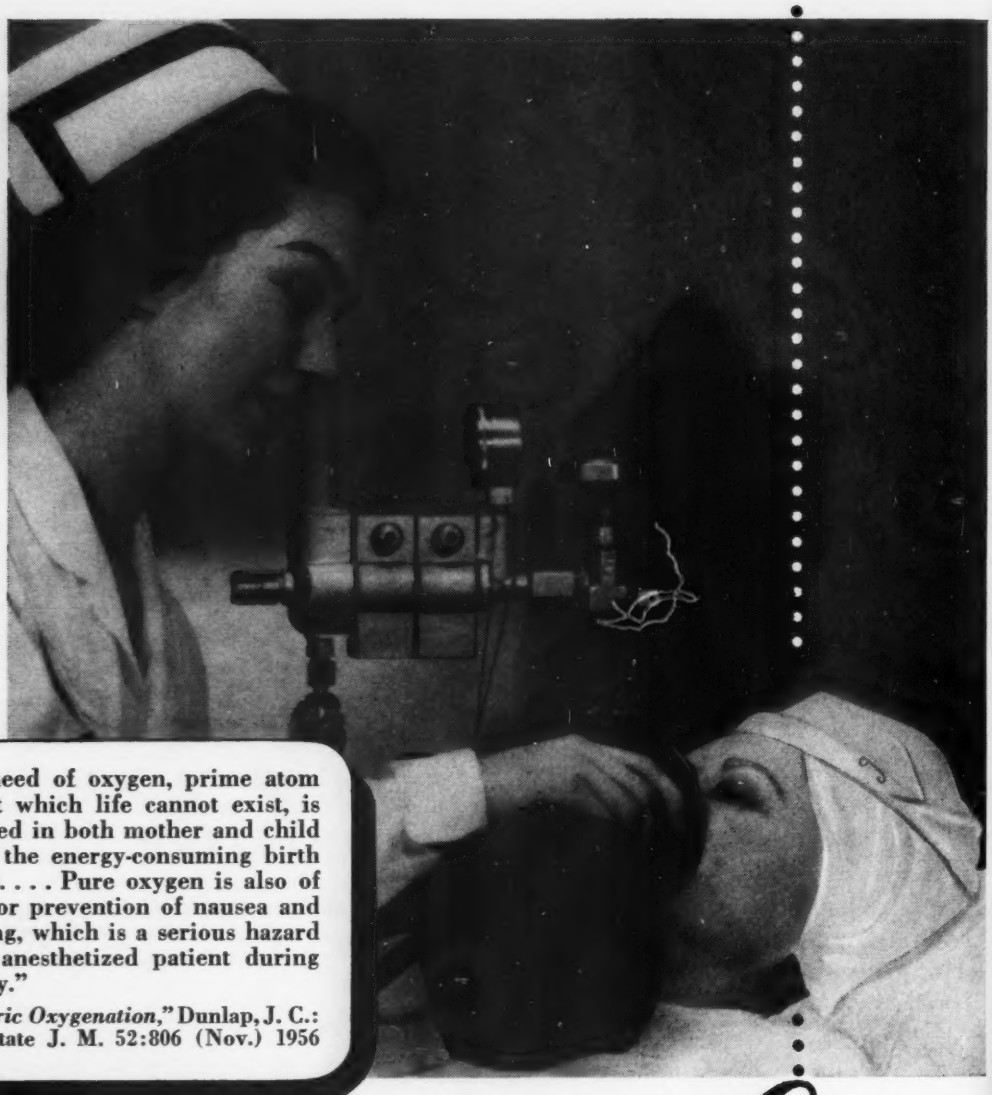

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1. Alexander, Edythe L.: Mod. Hosp., May, 1957.

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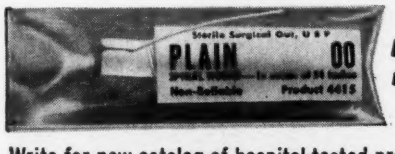

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1. Spiesman, M. G. and Malow, L.: Amer. J. Proctology, June 1956.

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1. Seegar, J.K.B.E., and Devlin, A.J.: Maryland M.J. *5*:330 (June) 1956.

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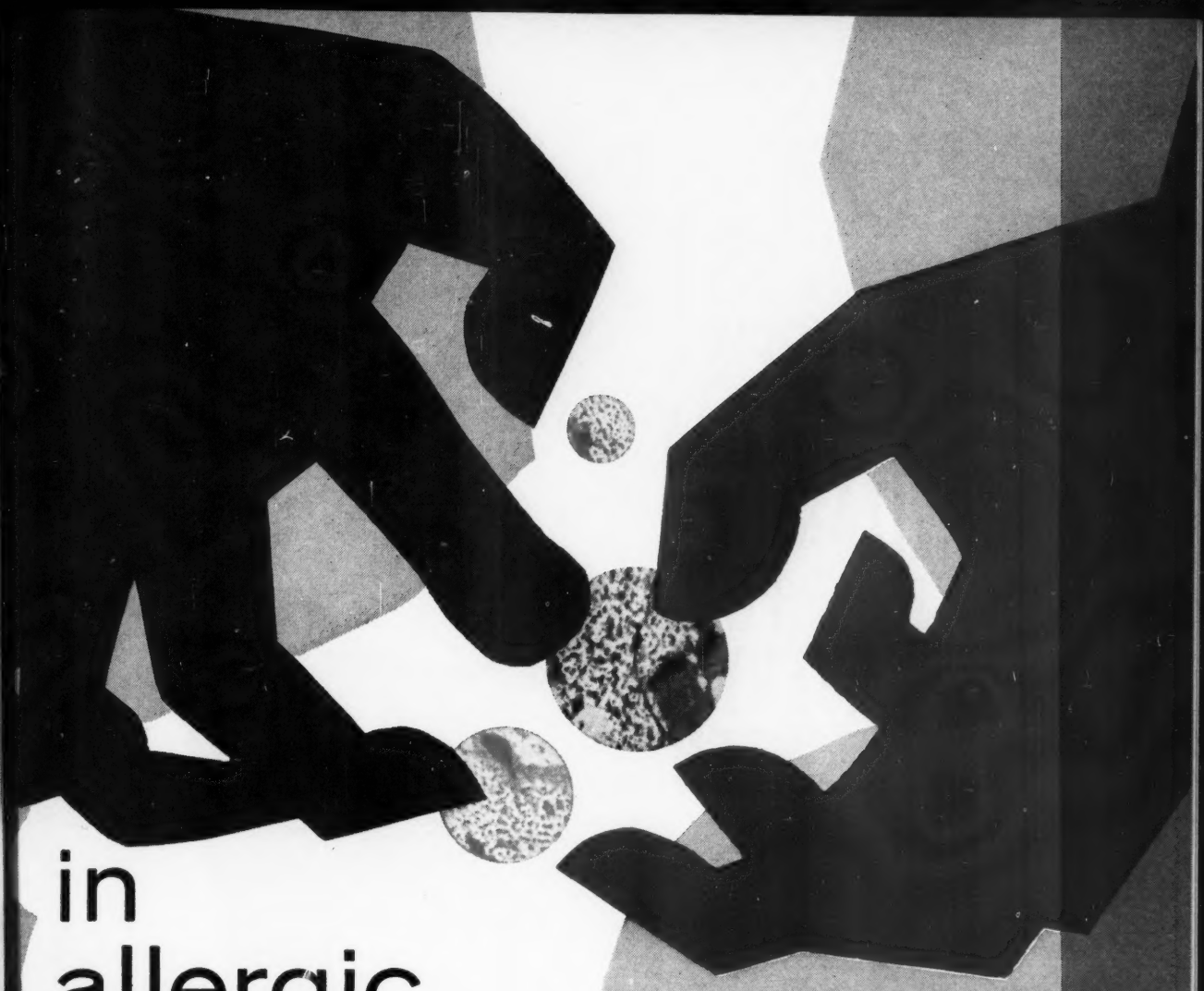

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Vol. 74, No. 5
November, 1957

American Journal of
OBSTETRICS AND GYNECOLOGY

Gynecology

THE PHASES OF THE MENSTRUAL CYCLE AND THEIR INTERPRETATION IN TERMS OF THE PREGNANCY CYCLE

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(From the Department of Embryology, Carnegie Institution of Washington)

THE introduction of the rhesus monkey into the study of sex cycles by Corner[1] in 1923 and his demonstration that its menstrual cycle is fundamentally similar to the cycle in the human made possible the experimental analysis of the menstrual cycle. Rhesus has also provided fully controlled and close series of normal uteri for detailed histological and chemical studies. The correlation of ovarian and uterine changes by the study of serial sections of both ovaries has demonstrated the range of variability during the cycle. Rhesus is unique in that the sequence of endometrial changes has been established by long-continued and detailed observations on living transplants.[2, 3]

The viewpoint of the gynecological clinic has continued to dominate discussions of the cycle to the neglect of the pregnancy cycle. The distinctive events of the menstrual cycle can be interpreted only in the light of the early stages of pregnancy. This was made possible by the collection and study of a series of early rhesus ova and embryos in the Carnegie Laboratory of Embryology by Hartman, Streeter, and Heuser. With this background, Hertig and Rock were able to initiate a new epoch in human embryology. The deciduae verae of their early stages have provided manifestly normal endometria for the control of the corresponding nonpregnancy stages. In other phases of the cycle, comparisons with rhesus uteri are necessary to distinguish between normal changes and such as are due to the abnormal conditions which justified surgical interference.

The current terminology of the cycle in the human species has not merely been outmoded by the more complete understanding of the controlling mechanisms; it suggests fundamental differences from other mammals and involves certain misinterpretations. A terminology is to be preferred which reflects the knowledge of early stages of development, the histological detail revealed by special methods, as well as the wealth of endocrinological evidence that has accumulated during the past 40 years.

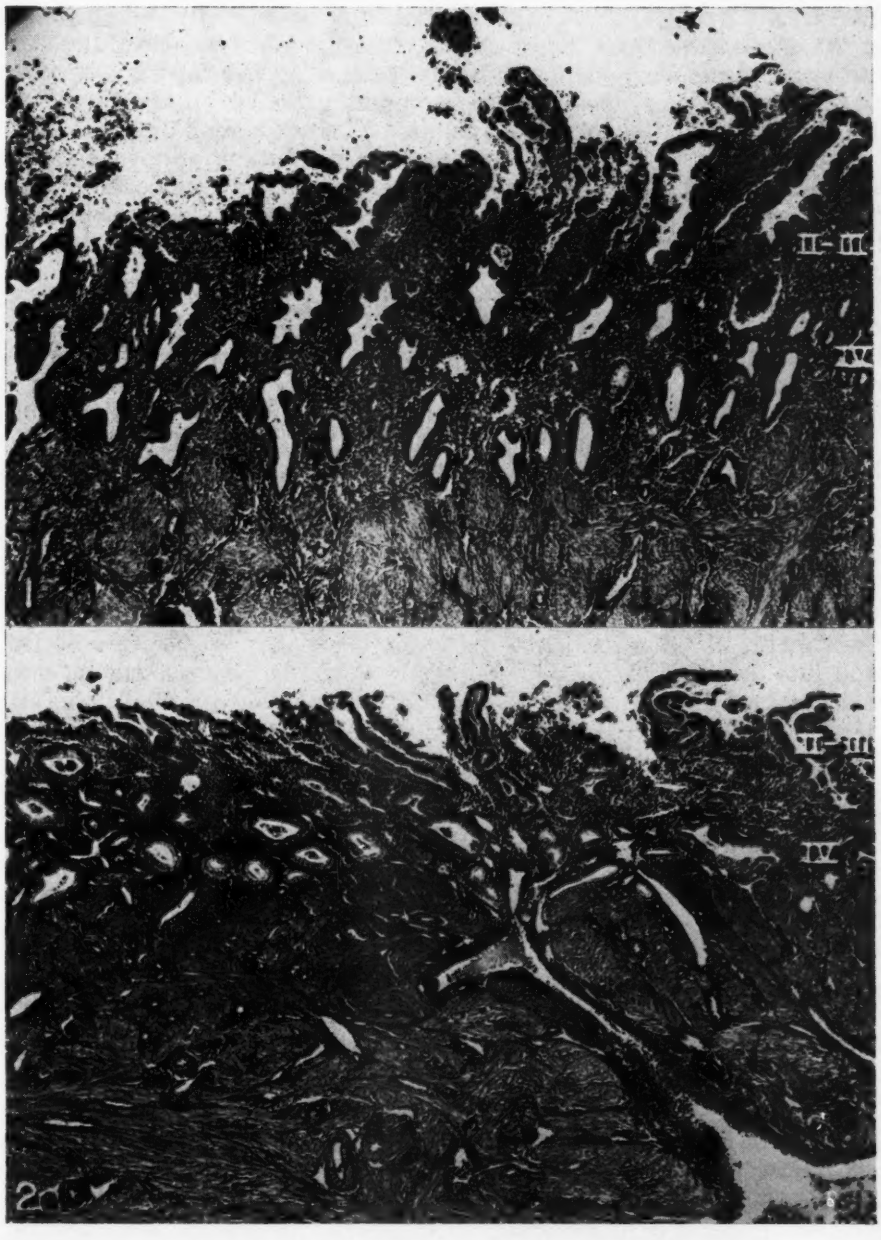
The terms introduced by R. Schroeder[4] have come into general use largely because the diagnostic features he employed are manifest under low powers of the microscope. The unsubstantiated deductions implied in this terminology call for an examination of the evidence. The term "proliferative phase" is based primarily on two features: (1) the superficial resemblance of the endometrium at the end of menstruation to the basal zone of the progravid phase and (2) the presence postmenstrually of epithelial mitoses which are accepted as evidence that three fourths of the endometrium is being regenerated.

The Endometrium at the End of Menstruation

In routine sections stained with hematoxylin and eosin, observed under low powers of the microscope, there is a certain resemblance between the involuted mucosa of late menstruation and the "basal" zone of other phases. This is particularly true of menstruation following anovulatory cycles as shown in Fig. 42 of Bartelmez and associates.[5] Since there is good evidence that such cycles are not rare in women,[6] it may well be that endometria like that shown in Schroeder's[7] Fig. 110 are instances of anovulatory menstruation. In the absence of specific staining of the reticulum, they seem to provide good evidence that all but the basal zone is shed during menstruation. Those who have advocated this interpretation have consistently ignored the extensive involution which characterizes the process of menstruation. Involution was recognized by Westphalen,[8] Hitschmann and Adler,[9] and subsequently by Frankl,[10] Bartelmez,[11, 12] and Sturgis and Meigs.[13] When the involution of the tissues and the cells of the endometrium is appreciated, it is clear that general appearances are misleading. Evidence of the extent of tissue loss is provided by the structure of the stroma. The distinctive connective tissue fibers of the basal zone make it possible to recognize the extent of this zone throughout the cycle when the reticulum is specifically stained. The fibers are coarser and more abundant than in the superficial zones.

Fig. 1 is taken from a human uterus obtained on day 1 following an ovulatory cycle which presented a series of stages from the prehemorrhagic "ischemic" phase to extravasation and on to shedding.* In this series of stages, most of the reduction in thickness had occurred in the superficial half of the endometrium which had lost over one-fifth of its thickness between the earliest and latest stages presented (see Fig. 2 of Bartelmez[11]). In the area shown in Fig. 1, the slough had separated; 3 zones can be recognized in the surviving mucosa: (1) a superficial disorganized zone where the reticular framework is fragmented and stains feebly or is gone entirely, (2) a zone with delicate fibers in the stroma and with glands of the collapsed progravid type, and (3) the "basalis" with its coarse reticular fibers. Estimates of the diameter of reticular fibers superficially average 0.7 μ; basally the average is 1.3 μ. In this instance the gland cells of the basal zone are not hypertrophic as they are

*Such series of stages have been described repeatedly in Homo. Their occurrence in rhesus monkeys[2, 5] indicates that the phenomenon cannot be set aside by dogmatists as "pathological."



Figs. 1 to 9 are taken from human uteri removed at laparotomy by the late Carey Culbertson, M.D., with especial care to prevent pressure on the endometrium.

Fig. 1.—Area of endometrium obtained at onset of flow, which appeared 28 days after an ovulatory cycle. Subtotal hysterectomy for fibromyoma on 25-year-old gravida i. Corpus uteri presented a series of stages from prehemorrhagic "ischemic" phase to the stage of shedding shown in this figure which does not include slough (see Bartelmez,[11] Fig. 2). Zones are indicated by Roman numerals (see footnote, p. 934). Zone IV ("basalis") is delimited by characteristic coarse reticular fibers. In zone III, glands show collapsed progravid form. Culbertson Collection, No. 83. (×50.)

Fig. 2.—Area of endometrium obtained on day 4 of menstruation which had appeared as expected. Subtotal hysterectomy for fibromyoma on 35-year-old gravida iii, para 0. Zone III recognized by its glands which show progravid form, as well as by its wide-meshed, delicate reticulum. Many glands in zone IV dilated with secretion, coagulated and shrunken by fixation and dehydration. In adjacent areas loose disorganized zone is being covered by epithelium spreading from gland mouths (see Bartelmez,[11] Fig. 4). Reduction in thickness, compared to that in Fig. 1, is accounted for by loss of ground substance from stroma, secretion from glands, and by general reduction in size of all cell types. Culbertson Collection, No. 161. (×50.)

in some premenstrual and early menstrual endometria. In subsequent stages of menstruation, these three zones can be recognized in uteri carefully removed so as to avoid mechanical injury to the mucosa. Fig. 2 presents a section of a uterus removed at the end of a flow, as is demonstrated by the spread of epithelium from the mouths of some glands. The reticulum preparations show three zones, as in Fig. 1, despite the continued involution. Superficially, many reticular fibers are fragmented. The average of 22 fibers stained deeply enough to measure is 0.6 μ; basally it is 1.2 μ. The difference in the total thickness of the 2 endometria is due chiefly to the disappearance of ground substance from the stroma. Thus, in the specimen from day 1 (Fig. 1), the average number of stroma cells is 228 per 100 μ^2 and 303 in that of Fig. 2. There is also a reduction in the size of the endometrial cells.[11, 14] In addition, the loss of secretion with the collapse of the glands plays a role. Loss of water from the mucosa in menstruation was found by van Dyke and Ch'en[15] in analyses of 13 entire rhesus endometria. The gram percentage of dry weight averaged 3 per cent more on day 1 than during the progravid phase. In human material, McLennan and Koets[16] similarly found the highest percentages of protein in endometria from the end of menstruation. Microchemical estimates of water content have little significance in comparison with macrochemical determinations such as these.

The presence of tissue overlying the basal zone* has often been recognized in early stages of menstruation.[17] It has been assumed that later during the flow the superficial tissue crumbles away leaving only the basal zone. Isolated cells and bits of tissue at the denuded surface are usually present in carefully removed uteri. They can readily be explained as adherent bits of the original slough. Sekiba,[18] Gobert,[19] and Bartelmez[12] have studied reticulum preparations of human endometria and have agreed that part of the "spongy" zone typically survives menstruation, even though there may be minute spots where the loss is greater. In a series of human uteri, the stroma cells at the denuded surface were found to be cytologically normal.[20] Further evidence as to the extent of tissue loss was provided by Markee's[2] continuous observations on 432 menstrual cycles in living transplants of rhesus endometrium. He did not see any cells being lost from the surface after the initial shedding. The progressive reduction in the area of individual transplants which he measured is due largely to continued loss of ground substance from the stroma.[21] Since the evidence that three fourths of the endometrium is shed is not valid, the extent of replacement is not as great as is usually assumed.

Postmenstrual Mitosis

Since dividing cells have often been found postmenstrually, it has been assumed that the essential feature of this phase is proliferation. The statements of Westphalen[8] and von Numers[22] that mitoses may be entirely absent or rare postmenstrually have been generally disregarded. Attention has been focused on the epithelial cells. However, we do not know how often a given cell divides. No counts of stroma mitoses have been published. Five human endometria

*The precursors of the well-defined zones of the human decidua vera can be recognized in the nonpregnancy cycle, although the transitions are usually gradual. For convenience in description, these zones are referred to by Roman numerals. Zone I includes the surface epithelium and a narrow band of stroma which at first has the appearance of granulation tissue and lacks a reticular framework. It is the reorganized superficial zone of menstruation. In rhesus it can be recognized in all phases of the cycle.[5] Zone II corresponds to the stratum compactum; abundant stroma separates the glands. The earliest responses to hormone changes appear at this level. Zone III, with its crowded glands, foreshadows the stratum spongiosum. Zones II and III correspond to the "functionalis" of Schroeder and have a characteristic wide-meshed, delicate reticulum. Zone IV, the "basalis" of Schroeder, is distinguished by the abundant coarse reticular fibers which may accompany the coiled arteries into zone III. The gland cells begin to divide later than they do superficially. At the end of the progravid phase, the gland cells may become hypertrophic, as they often do in early pregnancy. They accordingly have the potency to respond to the hormones of the corpus luteum.

obtained shortly after the end of menstrual periods have accordingly been studied with particular reference to the stroma. The specimens are from the Carey Culbertson Collection, which comprises 325 uteri removed at laparotomy. Normal changes have been distinguished from the pathological by comparison with corresponding stages of rhesus material.

Specimen 1 was obtained from a 34-year-old nullipara on day 5, one day after the end of external bleeding. A subtotal hysterectomy was performed by Dr. H. O. Jones for fibromyomas and diffuse fibrosis uteri. The endometrium is 0.6 to 1 mm. thick. The areas not yet covered with epithelium are small. The epithelium is low columnar except at the edges of the sheets that spread out from the gland mouths where it is squamous; rarely there are two strata of flattened cells. The material was prepared for cytological study, so that there is no difficulty in distinguishing between the migrating epithelial and the adjacent stroma cells.

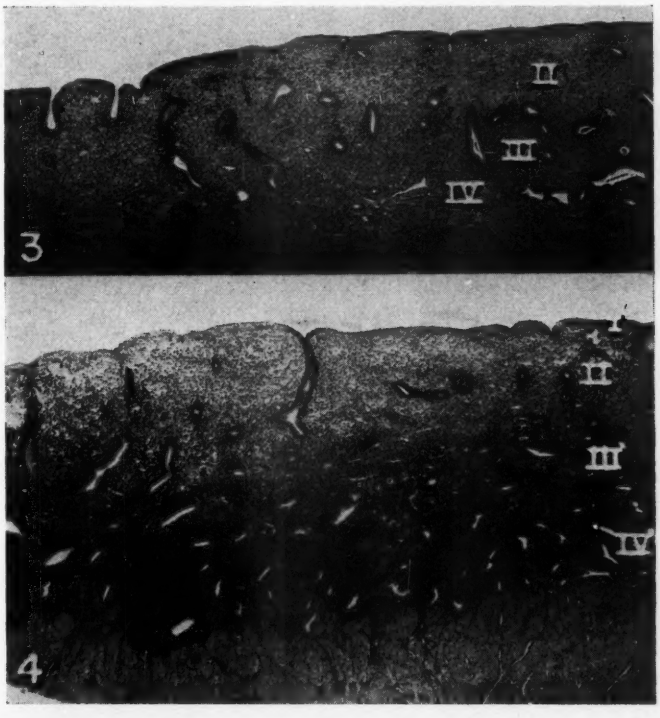


Fig. 3.—Area of corpus uteri from Specimen No. 1 obtained on the day after the end of external bleeding. Surface epithelium complete in area figured. Zone IV and surviving part of zone III can be clearly defined by their distinctive reticulum. Transitions from disorganized hemorrhagic zone of menstruation (Fig. 5) to granulation tissue characteristic of the early zone I (Fig. 6) show that this zone also persists after a flow. Coagulated secretion in basal glands at right. Culbertson Collection, No. 313. (×25.)

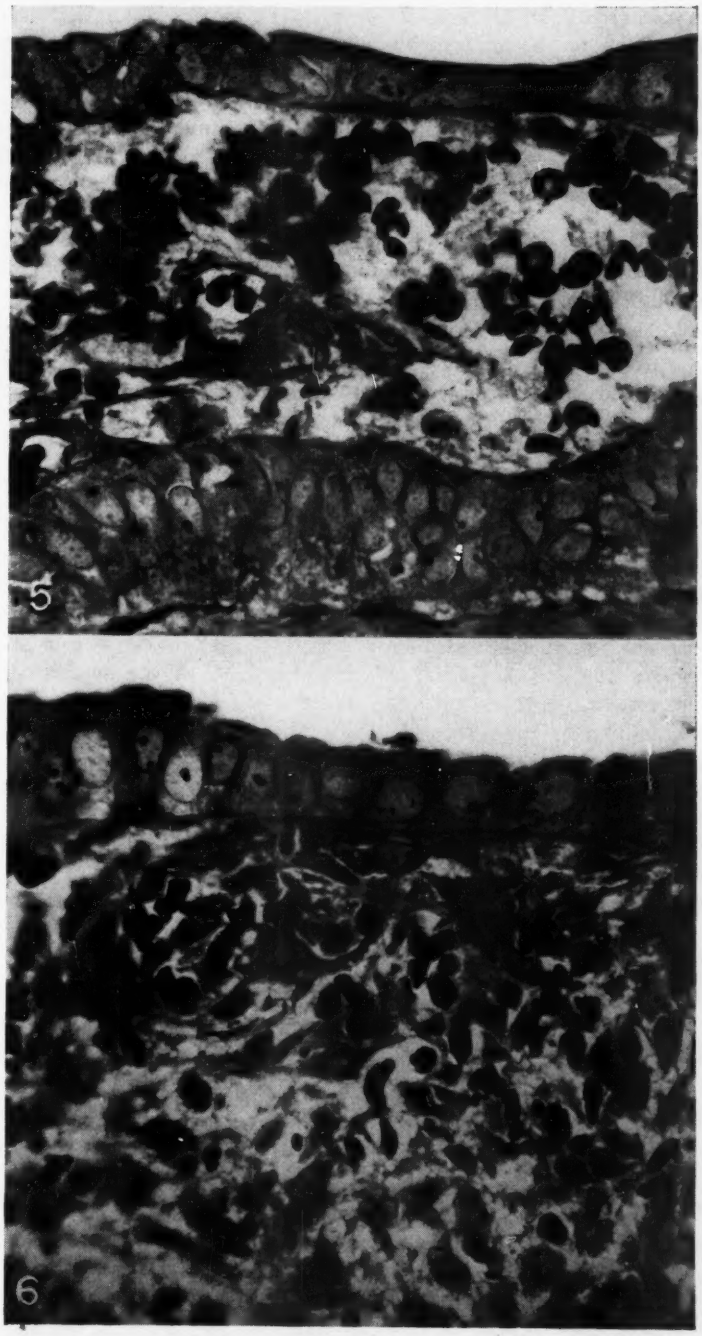
Fig. 4.—Area of corpus from Specimen No. 2 obtained on day 6 of cycle. Zone I characterized by transitions from disorganization to granulation tissue. Zone II can be distinguished from zone III by looser stroma and fewer glands. Zone IV is defined by its reticulum. Culbertson Collection, No. 272. (×25.)

As in the specimens taken during menstruation, three horizontal zones can be recognized (Fig. 3). The stroma of the most superficial zone varied in different areas, presenting a series of progressive changes from late menstrual conditions (footnote, p. 934). In the area shown in Fig. 5, the epithelium had spread over the disorganized hemorrhagic surface. The superficial circulation had probably been re-established, for Markee[2] observed this to occur at the time of re-epithelization. In some areas the subepithelial zone stained intensely in silver preparations as in late menstruation (Bartelmez,[12] Figs. 36 and 37) and the cells are sometimes dispersed (26 to 50 per unit area), as they are at the ragged menstruating surface.

TABLE I. DATA ON CELL DIVISION AND STROMA DENSITY IN A SERIES OF HUMAN ENDOMETRIA FROM THE REPAIR AND EARLY FOLLICULAR PHASES

SPECIMEN NO.	THICKNESS OF MUCOUS MEMBRANE (IN BLOCK)	DAY OF CYCLE	SUPERFICIAL STROMA MITOSES (ZONES I, II, III)	DENSITY OF STROMA CELLS PER 100 μ^2		EPITHELIAL CELL MITOSES				WANDERING CELLS (ZONES I, II, III)
				SUPERFICIAL (ZONES I, II)	BASAL (ZONE IV)	ALL EPITHELIAL CELLS	SURFACE EPITHELIUM	SUPERFICIAL GLANDS	BASAL GLANDS	
1	1 mm.	5	1 in at least 75,000 cells	26 to 156 18 areas average, 90	105 to 142	0.75% among 6,285	0.7% among 3,133	1.4% among 1,943	0 among 1,209	1.8%
2	1.7 mm.	6 or 7	2 in at least 22,000 cells	47 to 128 average, 84	Circa 300	0.8% among 6,972	0.88% among 3,400	1.4% among 1,788	0 among 1,784	3.7%
3	2.1 mm.	7	13 in at least 40,000 cells	25 to 100 average, 60	Circa 260	1% among 8,598	0.42% among 3,300	1.45% among 4,707	0 among 572	5.4%
4	2.3 mm.	11 (7 after end)	23 in at least 22,500 cells	23 to 48 average, 36	Circa 153	2.5% among 9,875	1% among 7,443	3.6% among 2,000	1.85% among 432	10%
5	2.7 mm.	11 (7 after end)	57 in more than 12,700 cells. Less than 0.45%	18 to 115 average, 51	Circa 168	3% among 4,968	3.26% among 2,974	3.9% among 1,390	3.3% among 604	10%

In other areas the cytoplasm of the stroma cells has increased. They are crowded, as in young granulation tissue (Fig. 6), and the cell density ranges from 100 to 156 stroma cells per $100\mu^2$. In addition, lymphocytes, macrophages, and rarely a mononuclear granule cell are present (Table I). In the most advanced spots, stromal ground substance has increased,



Figs. 5 and 6 from same endometrium as Fig. 3. Photomicrographs with Zeiss 3.0 mm. apoch. immersion objective, ap. 140, oc. 4. (×750.)

Fig. 5.—Disorganized hemorrhagic area covered by typically irregular surface epithelium. Wall of gland below; vacuoles in gland cells due to glycogen.

Fig. 6.—Subepithelial stroma (zone I) resembles granulation tissue. Red blood corpuscles uniformly black. Below, typically loose stroma of zone II.

the mucosa reaches a thickness of 1 mm., and there are 50 to 100 cells per unit area. It can be called zone I, for it does not differ from that of later repair stages (Fig. 4). It lacks reticulum except for the basement membranes of the glands. Between this superficial zone and the basal zone, reticular fibers are delicate and form a wide mesh in contrast to the abundant coarser fibers which characterize zone IV (''basalis''). Evidences of disintegrating reticular fibers in zones II and III are significant. The glands vary in form, and occasionally one is almost parallel to the surface. Secretion that stains with mucicarmine is present either in the lumen (see glands at right of Fig. 3) or in the cells. In some areas it is also present in the surface epithelium. The gland cells occasionally contain glycogen (Fig. 5). Here and there a gland is dilated basally, as in the follicular phase. There are some mitoses in the epithelial cells (Table I). In one of the 4 blocks surveyed, there were only 8 among 2,909 cells.* In the stroma, a search through 13 sections from the several blocks of tissue brought to light only a single mitosis. Obviously the superficial zone is not a new growth but has arisen through reorganization. The chief feature is the accumulation of stromal ground substance; the volume of many stroma cells has also increased. The glands keep pace with this expansion largely by cell division, since they show no sign of having been stretched as the mucosa thickened.

Specimen 2 came from a 26-year-old gravida vi, para iv. Menstrual discharge was present in the vagina on day 6 when a subtotal hysterectomy was done because of symptoms of salpingitis during the preceding month. The endometrium is 1.2 to 2.0 mm. thick. Zone I is as variable as in the preceding specimen. The surface epithelium is almost complete and lacks a basement membrane except at the gland mouths. There are areas where the ground substance of the stroma stains intensely; elsewhere the stroma is disorganized as at the left in Fig. 4. Groups of crenated red blood corpuscles mark menstrual extravasations covered by surface epithelium. In still other areas, the stroma cells are crowded and elongated parallel to the surface. They have but little visible cytoplasm, as is the case in other zones. Zone II is marked by few glands and an abundant ground substance precipitated in granular form. The reticulum of the interglandular stroma is absent except for occasional irregular fibers. These are frequently applied to the surface of macrophages. Degeneration of reticulum superficially is a feature of repair in rhesus (see p. 940), and in both species dedifferentiating arterioles can be found. The glands at this level tend to extend perpendicularly to the surface and have well-differentiated basement membranes. In zone III the glands are irregular in form and closer together; the stroma is denser. In most glands there is little coagulum, but in some it resembles that in Fig. 11. The basal zone is as dense as in menstruation (Table I), and the reticulum is coarse. Only 2 dividing stroma cells were found anywhere in the endometrium (Table I); there were 3 in the walls of blood vessels. The incidence of wandering cells, notably plasma cells, is low considering the infection. There are some recent extravasations, probably due to the preoperative bimanual examinations by interns and residents.

Specimen 3 was obtained from a 37-year-old gravida v, para iv, on day 7 of the cycle; a subtotal hysterectomy was done because of perisalpingitis. The endometrium varies from 1.6 to 3.1 mm. in thickness. The surface epithelium is almost complete, typically variable, the low columnar form predominating. Ciliated cells are common. The secretion in the glands has but little coagulable material in it, but it stains metachromatically. Rarely, a

*It is important that several blocks from the median area of the corpus be studied, since there is much variation in different areas, particularly in this phase. Uteri from laparotomies are preferable because trauma of curettage, vaginal hysterectomy, and biopsy introduce stromal changes which may lead to error. Postmortem material is worthless for all detailed histological and cytological studies.

In counting mitoses, it is necessary to study samples from several regions of the corpus because different blocks may show significant differences in the number of dividing cells, as Carter[23] has noted. In counting gland cells, it is necessary to include every favorably cut gland in a section so as to avoid the subconscious selection of glands with 1 or more mitoses in them. In repair stages, many glands have none at all. Since early prophases are the most frequent stages, they should be counted, and, for this purpose, an immersion lens is essential. Without it, degenerating leukocytes may be mistaken for telophase nuclei. In the present study, the earliest prophases included are those in which the nucleus and the chromosomal granules in the intact nucleus had begun to enlarge. In the case of stroma-cell mitoses, it is necessary to have serial sections so that they can be differentiated from dividing endothelial cells of tangentially cut capillaries.

few intracellular glycogen granules can be found (Fig. 11). Some basal glands are dilated with secretion (Fig. 7). Zones I, II, and III comprise four fifths of the thickness in some areas. In zone I there is no general reticulum, and the surface epithelium has no basement membrane. In zones II and III, the reticulum is in the form of a delicate wide-meshed net in silver preparations; many fibers stain feebly with Mallory. Fibers in a bit of tissue removed from zone II of a block in alcohol average 0.5 μ in diameter; from zone IV they average 1.3 μ. The corresponding averages for a 4 μ section stained by the Bielschowsky method are 0.68 and 1.38 μ. The ground substance yields only a feeble metachromatic reaction indicating a high water content. The transitions from zones II and III and from III and IV are gradual. Most of the blood (which appears black in Fig. 7) is menstrual in origin, as indicated by the crenated and fragmented red blood corpuscles.

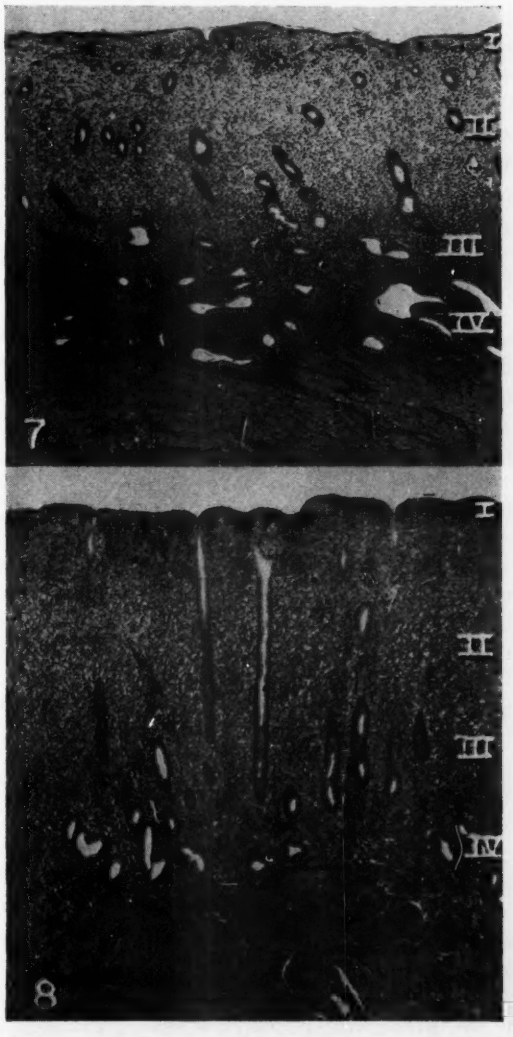


Fig. 7.—Area of corpus from Specimen No. 3 obtained on day 7. Zones of endometrium distinguished as in Figs. 1 to 4. Gradual transition from looser stroma of zone II to denser zone III. Many glands in zone IV dilated with secretion which yielded but little coagulum on fixation. Fragmented red blood corpuscles superficially appear as black dots. Culbertson Collection, No. 240. (×25.)

Fig. 8.—Area of corpus from Specimen No. 4 obtained on day 11, about a week after the end of a period. As a result of increase in stromal ground substance, zone II involves 60 per cent of the total thickness. Glands at this level are straight, having kept pace by mitosis and, to some extent, by cellular hypertrophy. Zone IV glands dilated with secretion. Culbertson Collection, No. 251. (×25.)

Specimen 4 was obtained on day 11, about a week after the end of external bleeding, from a 33-year-old nullipara who had had dysmenorrhea for a year. There was a mural fibromyoma and a small endometrial polyp. The normal endometrium is from 2 to 3 mm. thick and presents the typical picture of the early follicular phase (Fig. 8). Zones I, II and III now involve 85 per cent of the thickness, due largely to the increase in ground substance, and not to increase in the number of stroma cells (Table I). The surface still has a few defects in the epithelium, which is mostly 20 to 25 μ in height, but only 5 μ in spots. There is a film of secretion on surface and glandular epithelium which stains with mucicarmine and metachromatically with toluidine blue. Glycogen can also be demonstrated in the lumina of the glands and rarely in the cells. Superficially, the glands have kept pace with the expanding stroma by cell division, 2.5 cells per hundred being in mitosis (Table I). Some basal glands also have mitoses, but the great majority of cells at this level are secreting, and frequently there is a basal dilatation as is usually the case in the follicular phase. Near the surface, stroma cell mitoses are encountered more frequently than in the phase of repair; they are rare compared to epithelial mitoses. In zones II and III, a new delicate reticulum has appeared, but most of the intercellular space is filled with a granular coagulum. Coarse fibers distinguish the stroma of zone IV.

Specimen 5 came from a 30-year-old gravida iv, para ii. A painful peritoneal cyst called for the hysterectomy done on day 11, 7 days after the end of a flow. The endometrium ranges from 2 to 2.7 mm. in thickness and belongs to the early follicular phase, since no large follicle was noted at operation. The four zones are distinct, as indicated in Fig. 9. More abundant secretion in the glands indicates a later stage than that of No. 4. Zone I lacks a basement membrane, and sometimes the general reticulum is absent, as is the case in rhesus. Zones II and III are wider than previously, and a new reticulum has developed. The ground substance may be either granular or homogenous. Stroma mitoses had increased, so that their frequency could be expressed numerically. The values from sampling proved to be so variable that surveys of entire sections were indicated. In moving from field to field many interkinetic cells were not counted, whereas the prominence of the dividing stroma cells greatly reduced the likelihood of their being overlooked. The percentage of dividing cells (0.45) is certainly not too low. The great majority of stroma mitoses are in a zone 0.5 to 0.7 mm. below the surface epithelium. No indications of amitotic division were noted in this or in the other endometria studied. Zone IV in both Nos. 4 and 5 is approximately as wide as in Nos. 2 and 3 but comprises only 14.5 per cent of the total thickness. The relative thickening of zones I to III is accordingly due primarily to the increase in ground substance; the 45 dividing cells among 10,000 (Table I) could hardly play a significant role in the thickening. This contrasts with 400 new cells per 10,000 which provided for the elongation of the glands during this period.

Corresponding rhesus endometria serve as evidence that the significant changes described in the human specimens are normal events.

Repair Phase in Rhesus Monkeys

C128 was obtained on day 4 of the cycle, when the vaginal lavage had become practically free of blood. The preceding cycle was ovulatory. Resurfacing had just begun, and in such areas the 4 zones characteristic of other phases can be recognized. The general appearance is shown in Fig. 12. Transitions between the disorganized superficial zone of menstruation and zone I of the follicular phase, as well as the presence of zones II, III, and IV, clearly demonstrate the persistence of most of the "functional" zone. The stroma is still of the dense menstrual type (152 to 222 cells per unit area). No stroma cells were dividing, nor were mitoses present in blood vessels or basal glands. Among 7,000 epithelial cells, I noted 73 mitoses. The horizontal zones recognized in reticulum preparations are as follows: (1) the disorganized surface characteristic of menstruation, which is covered here and there by epithelium continuous with the ends of glands; (2) zone II has fewer glands than zone III; both of these are differentiated from

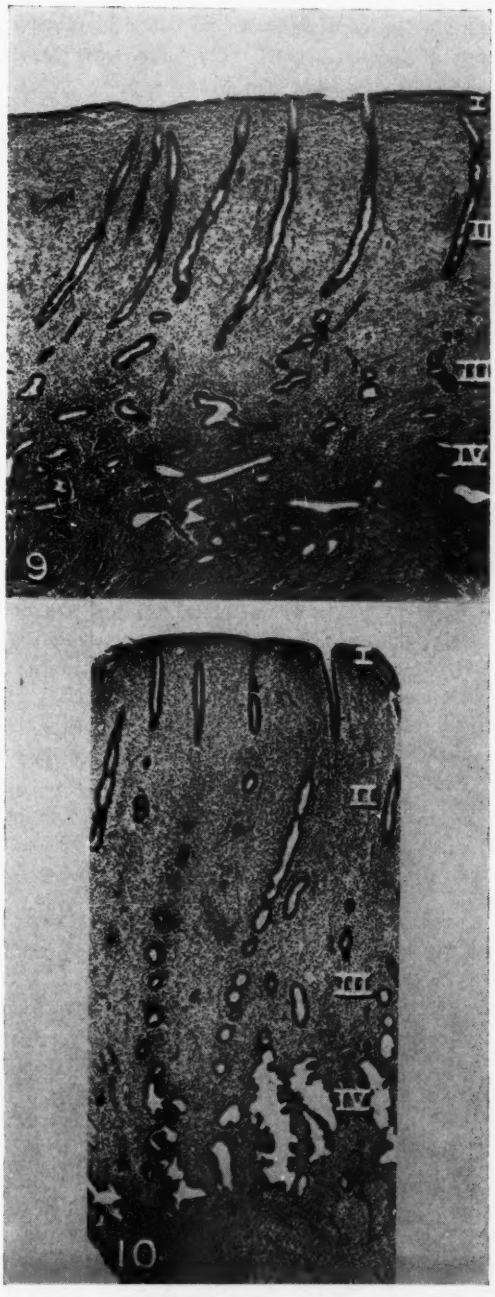


Fig. 9.—From Specimen No. 5. Hysterectomy on day 11, 7 days after end of menstruation. Straight glands in zone II. Typical follicular-phase endometrium. Secretion has accumulated in glands of zones III and IV. Culbertson Collection, No. 283. (×25.)

Fig. 10.—From Specimen B120, corpus uteri of rhesus monkey obtained on day 4 following ovulatory cycle. Advanced stage in repair. All four zones are differentiated; zone I has groups of crowded cells (dark in figure) reorganized from superficial zone of menstruation; zone II has a looser stroma than the others, and glands are farther apart; zone IV is distinguished from zone III by coarse reticulum and by its "budded" glands dilated with secretion, in which mucin and glycogen were demonstrated. (×25.) (From Bartelmez, Corner, and Hartman.[5])

zone IV by their delicate reticular fibers. The difference between them and the coarse fibers of zone IV is more apparent in Mallory than in Bielschowsky preparations because the overlay of silver is greater on the fine fibers. The coiled arteries are at the surface where there are indications of dedifferentiation.

B120 is also a fourth-day specimen but presents a later stage in repair. Most of the surface is covered with epithelium 20 to 25 μ tall, and the superficial circulation had been restored.[24] The mucosa reaches 3 mm. in thickness. The 4 zones characteristic of the follicular phase are present (Fig. 10). It is clear that during the preceding ovulatory flow not more than zone I and part of zone II had been shed.[5] The dense superficial stroma of menstruation is present below the epithelium in some spots. They appear as darker areas in Fig. 10. Elsewhere the stroma cells have enlarged and present the picture of granulation tissue. The stroma in zones II and III is loose (mostly 50 to 86 cells per 100 μ^2). They are differentiated from zone IV by their delicate reticulum and from one another by the disposition of the glands. The glands of zone IV are dilated and appear to be budding. This type of basal gland is also present in the endometrium of Fig. 18. No mitoses are to be found in the stroma; zones II and III are thicker and looser than in the preceding specimen because of the increase in ground substance. The corresponding lengthening of the glands is due largely to cell division. In zone IV there are no mitoses.[25] Glycogen and mucin are present in the epithelial cells and in the lumina of the glands.

C125 was obtained on the day following a 6 day flow. It resembles No. 3 of the present human series in many respects. The four endometrial zones are obvious under low magnification (Fig. 1 of Bartelmez and associates[5]), and the evidences of secretory activity are as abundant as in the preceding specimen. Most glands in zones III and IV are dilated with secretion. In a survey of 6 sections, mitoses were found in 6 stroma cells and 9 in capillary endothelium. In zones II and III, one can often find reticulum fibers ending in rows of granules, indicating that the fibers which survived menstruation are disappearing. The intact fibers in these zones are dispersed and slim. The diameter of a number of them was estimated in Mallory preparations; the average value was 0.8 μ; in zone IV they varied from 1.2 to 1.5 μ.

Comment

The endometria from the phase of repair, described above, give evidence both in Homo and rhesus that the three zones usually recognizable at the end of a menstrual period become more clearly defined after the epithelium has begun to spread over the surface. The chief factor in the differentiation is the loosening of the middle zone by the increase in ground substance of the stroma (Figs. 3, 4, 5). This would coincide with the return of a more active circulation, as observed by Markee[2] in ocular transplants. Significant stroma cell proliferation by either mitosis or amitosis, such as is currently postulated, is absent in the human and rhesus specimens described (Table I) and in others recorded in the literature. Thus, Westphalen's[8] observations on the absence of mitoses postmenstrually are significant, even though he did not make estimates of the number of cells observed. He studied mitosis in 50 normal, perfectly preserved human endometria (most of them curettings) and reported on his specimens individually. In 8 endometria from the first 3 days after the end of menstruation (days 5 to 11 after the onset), he found no mitosis in stroma or blood vessels. Similarly, von Numers[22] noted "few" mitoses in either the stroma or epithelium of 5 endometria from days 4 to 8 of the cycle. There are statements that dividing stroma cells may be present during this period. None of them, however, involves cell counts. Thus, Westphalen found "some" dividing cells in 3 specimens obtained on days 6, 6, and 12, respectively. Hitschmann[26] said that postmenstrually mitoses "can be demonstrated in the stroma." Hertig[27] made a similar statement. Noyes, Hertig, and Rock[28] indicate in their graph

that mitoses are present in the stroma at the end of menstruation and that they gradually increase subsequently. They do not include stroma mitoses among the criteria of their "early proliferative phase," which corresponds to the phase of repair, as defined above. How abundant they were is indicated by the surveys and the cell count recorded in Table I. Dividing gland cells are also reported in repair stages by Westphalen, and by Bensley[25] in late stages of menstruation in rhesus on the basis of cell counts. This is an indication of a rise in available estrogen,[23] which Markee and Berg[29] found increased during menstruation in women as compared with the premenstrual (ischemic) phase. The time at which such a rise occurs varies, as all other features of the cycle vary, with the individual and the particular cycle. The most striking evidence of this is provided by the careful measurements made by Gillman and Gilbert[30] on the perineal area of the chacma baboon. They found that in 80 per cent of the animals the estrogen-controlled swelling began sooner or later during the menstrual flow, but in other instances not until days after the end of a period. Markee's observations on prehemorrhagic stasis show that the tissue injury usually ascribed to menstruation begins before menstruation and during extravasation. It is accordingly not surprising to find evidences of increased ovarian activity during menstruation.

The 3 human endometria obtained shortly after the end of menstruation provide evidence that epithelium from the gland mouths spreads over the ragged hemorrhagic surface, which is reorganized as zone I (Figs. 3, 4, 5, 6). The deep staining with silver, which characterizes the menstruating surface, persists briefly in zone I after resurfacing (Bartelmez,[12] Figs. 26 and 27). In Specimens 1 and 2, there are more advanced areas where the cytoplasm of the stroma cells in this zone has increased so that they resemble the fibroblasts of granulation tissue (Fig. 6). Between the subepithelial zone and the basal zone IV, much ground substance accumulates so that the stroma cells are well separated (Fig. 3 and Table I). The average in this zone in Specimen 1 is 90 stroma cells per 100 μ^2 as compared with 303 in the fourth day specimen of Fig. 2. While the ground substance is increasing, stromal mitoses are very rare. The glands, on the other hand, keep pace by straightening and by cell division (Table I). At this time the number of gland cell mitoses is not great (14 per 1,000). *They are all superficial;* no mitotic activity can be found in the clearly defined zone IV ("basalis"), which varies but little in absolute thickness during postmenstrual phases. Relatively, it keeps decreasing; at the end of menstruation it comprises one third to one half of the thickness; a week later it is only one seventh (compare Figs. 2, 8, and 9). During this period the increase in ground substance is greater in the zone adjoining the subepithelial zone (zone I), so that the distance between glands increases. Zone II can accordingly be distinguished from zone III, in which the glands are closer together (Figs. 2, 7, 8, 9). In rhesus the menstrual loss is usually less than in Homo, so that both zones II and III are obvious in all stages of menstruation, especially after ovulatory cycles (Fig. 10). In both species the superficial reticulum of the stroma dedifferentiates and then redifferentiates; such enzyme-controlled processes may be rapid.[31] Similar changes occur in the superficial rami of the coiled arteries. These will be described elsewhere.

Follicular Phase.—During this phase the replacement of cells lost or injured during menstruation becomes more prominent than during repair. It is almost entirely confined to the epithelial cells; in the stroma it is negligible (Table I). More cells are found dividing toward the end of the phase, and the glandular epithelium becomes pseudostratified. There are no data as to the rate of division. There is no indication of the rapid growth exhibited by embryos

and tumors. The current dogma which emphasizes cell division and postulates the regeneration of three fourths of the endometrium postmenstrually has been a factor in diverting attention from evidences of secretory activity during any other than the "secretory" phase (Fig. 11). Both mucicarmine-positive substance and glycogen were demonstrated in human endometria of this period by Bartelmez and Bensley,[32] who also described a basophilic substance in the vicinity of the nucleus in the follicular and progravid phases. Atkinson and Engle[33] identified this as ribonucleic acid. The presence of a substance containing RNA and glycogen as well was confirmed by McKay and co-workers,[34] who found that the alkaline phosphatase reaction reaches a maximum in the gland cells "at mid-cycle." There is greater variability in the series described by Hall.[35]

In rhesus the glandular secretion becomes prominent as the Graafian follicles approach maturity. In human material it is impossible to distinguish histologically between endometria obtained shortly before, during or soon after ovulation. The correlation of uterine and ovarian findings in rhesus makes it clear that follicular development may begin earlier or later in a cycle; ovulation may occur earlier or later. Consequently the picture presented by the endometrium at ovulation varies appreciably.[5] In routine material of the follicular phase, there is often only a shriveled mass of coagulum at one side of the gland lumen, and consequently it does not appear in many glands present in a thin section. This has led to the naïve statement that the glands are "empty." The fact that the water content of the secretion is high does not militate against its possible physiological significance. The blebs which arise on the gland cells (Fig. 11) indicate the presence of an intracellular secretion antecedent. They are small and inconspicuous compared to the protrusions which similarly arise in the progravid phase between the time the blood supply is cut off and the fixative reaches the cell.[36] During most of the follicular phase, the glands are dilated by accumulated secretion in the basal zone only (Fig. 9).

The quantitative chemical analyses of the endometrium have demonstrated secretion during the follicular phase, since histologically glycogen is found to be confined almost entirely to the glands. The other component of the secretion is generally assumed to be a mucin, since it gives characteristic tinctorial reactions, but it has not yet been characterized chemically. It may be that the two components have not been entirely separated in the chemical analyses, but they nevertheless confirm the presence of secretion which the histological preparations demonstrate in all phases of the cycle. The macrochemical analyses of rhesus uteri by van Dyke and Ch'en[15] were fully controlled by histological studies of uterus and both ovaries. They found an average of 2.2 per cent glycogen (dry weight) in 5 endometria associated with large normal Graafian follicles. In 6 endometria under the influence of active corpora lutea, the corresponding value was 3.4 per cent. Spyker and Fidler[37] analyzed 15 human endometria which they identified histologically as "proliferative." In some of these, the glycogen values were higher than in certain specimens from the "differentiative phase." The presence of some glycogen in early stages of the cycle is indicated in all studies listed in their summary. More recently, Arronet and Latour[38] reported their findings in individual specimens, so that the range of variability can be appreciated. In 4 endometria diagnosed histologically as "proliferative," they obtained glycogen values of from 0.37 to 0.45 gram per cent of wet tissue. In 2 from days 16 and 17, the values were 0.69 and 0.56 per cent, although in others from these days the maximum values for the entire cycle (2.0 per cent) were obtained. It is unfortunately impossible in human material to say whether the specimens with the lower values preceded or followed ovulation. In any case, it is obvious that in Homo as in rhesus there

is glycogen in the endometrium before ovulation. The intimation that significant production of secretion is confined to the phase dominated by the corpus luteum is manifestly not justifiable. Attention must also be called to the practice of assigning specimens in human series to the follicular ("proliferative") phase simply because they do not have the characteristics of either the progravid or the menstrual phase. In rhesus, where both ovaries are available for study, it is obvious that the absence of the distinctive features of the follicular phase in an "interval" endometrium indicates ovarian inactivity which may continue for days or weeks, or a ripe egg may never be produced during the particular cycle. The inclusion of such specimens in the follicular phase unduly lowers the average values obtained for the phase and seriously complicates the interpretation of the findings.

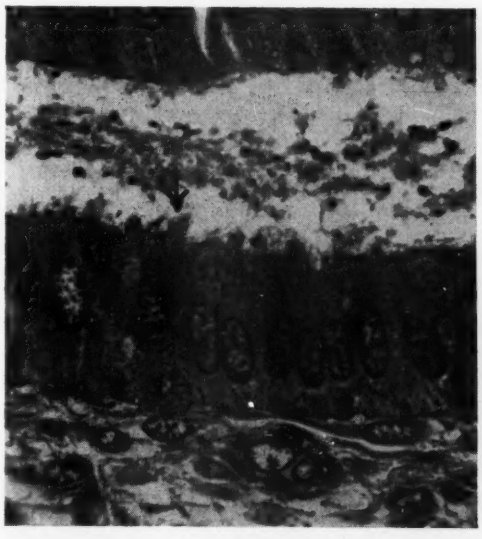


Fig. 11.—From a human uterus obtained on day 8, about 4 days after the end of menstruation. Hysterectomy on 26-year-old gravida viii, para vi, because of pyosalpingitis and fibrosis uteri. Part of a gland in zone II. Abundant secretion coagulum in which both glycogen (deeply stained granules) and mucin were demonstrated. The blebs (arrow), which project beyond the terminal bars of gland cells, are artifacts which arise between the time the blood supply is cut off and the fixing agents arrive. They indicate the presence of secretion antecedents in the cytoplasm. Note the characteristically loose stroma. Culbertson Collection, No. 167. (3 μ section stained with hematoxylin and eosin. Optical system as in Figs. 5 and 6. ×750.)

Experimental and histological studies on many mammals have abundantly demonstrated that the preovulatory period is dominated by estrogen and associated with one or more rapidly growing ovarian follicles. There is no reason why the widely used term "follicular phase" should not be applied to this phase in Homo. In rhesus it can be accurately identified by the ovarian findings and is characterized by certain features which can be summarized as follows:

1. A metachromatically staining ground substance develops in the stroma of all zones during the phase, especially in zone II (also in Homo[39]). This is the chief factor in the thickening of the endometrium.

2. The glands are straight superficially with narrow lumina. Basally they are usually dilated with accumulated secretion (Figs. 7-9).

3. The secretion frequently has but little coagulable substance. It nevertheless contains both glycogen and mucin. Toward the end of the phase, it is as dense as that in Fig. 11 taken from a human endometrium.

4. Mitoses become increasingly abundant during the phase, reaching a maximum shortly before ovulation. They are always far more abundant in the epithelium than in the stroma. There is no evidence as to the *rate* of cell division; it is not necessarily rapid.

5. Toward the end of the phase, there is a diapedesis of red blood corpuscles which sometimes reach the vagina (intermenstrual bleeding).

Progravid Phase.—Under the influence of the corpus luteum, the amount of glycogen and mucin in the secretion increases, and it yields an abundant coagulum on fixation, so that it becomes a prominent feature of the endometrium. The secretion accumulates in the glands which dilate and then sacculate. This does not prove that the rate of secretion has increased. The accumulation can be directly correlated with myometrial changes produced by progesterone. Under its influence, the contraction waves become localized and reduced in amplitude. The myometrium relaxes as described in Part II of Reynolds'[40] *Physiology of the Uterus.* Clinically the uterus softens and enlarges in rhesus[41] and in women.[42] Figs. 14 and 16 illustrate the difference in thickness of endometrium and myometrium in the follicular and the progravid phases. It appears then that the progravid phase is distinguished by myometrial activities which result in the retention of secretion within the glands.

When the early stages of development of the rhesus egg were obtained in the Carnegie Laboratory, it was obvious that there were no important differences between early pregnancy and nonpregnancy cycles. The human preimplantation stages of the endometrium are also similar to the corresponding nonpregnancy stages when the normal range of variability is taken into account.[43] Even in early implantation stages, there is but little difference between the two. The terms for the phase introduced by Corner,[44] namely, "progravid" or "progestational," are valid and appropriate. The term "luteal," like the other two, does not imply that the secretion of the follicular phase is negligible. The objections to it are that the yellow ("lutein") pigment does not become obvious until the activity of the corpus luteum has begun to wane, that this pigment does not develop in most mammals, and that it seems to have no physiological importance.

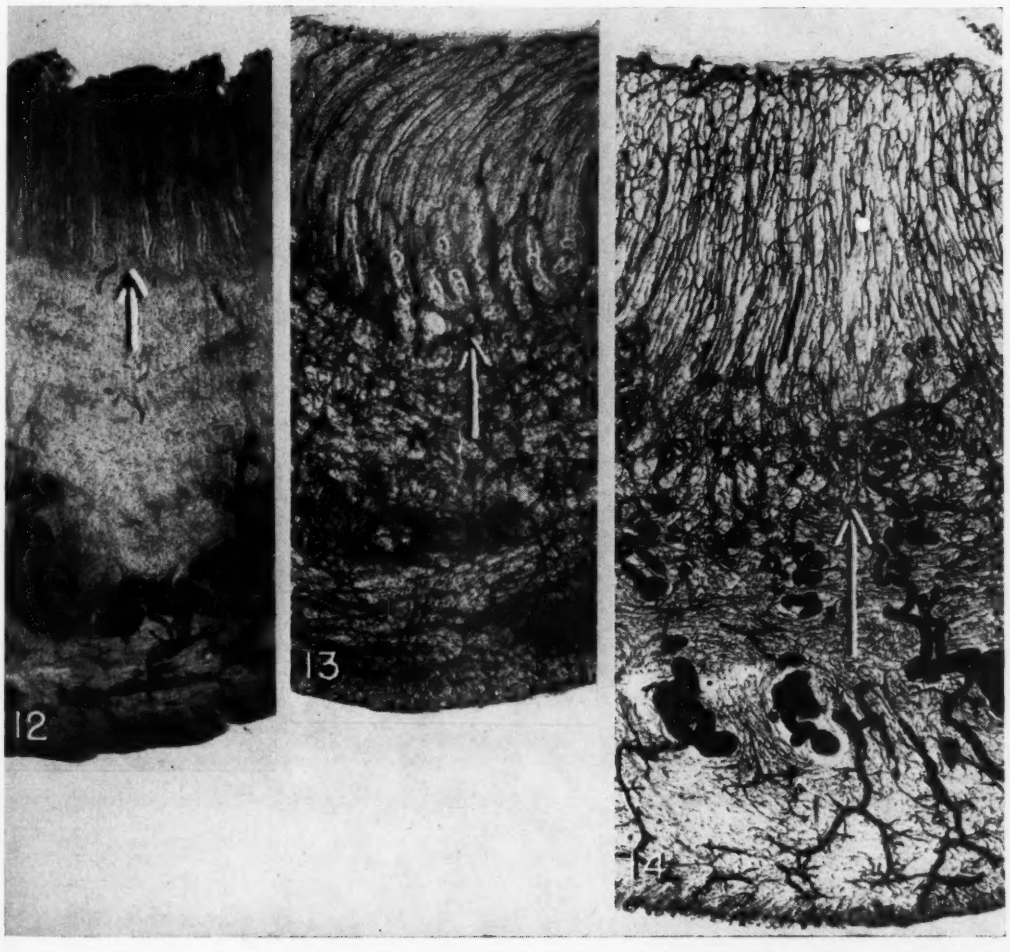
Correlated Changes in Endometrium and Myometrium.—

When endometria are grouped on the basis of the ovarian findings, it is clear that within each group there is variation in thickness. Since the current diagrams of the human cycle are based on series of individual specimens, the indicated changes in thickness necessarily represent general impressions, as well as guesses as to the time of ovulation. Rock and Bartlett[45] and Hertig,[27] recognizing the inadequacy of the criteria for seriation in general use, assigned their specimens to particular days of a theoretical 28 day cycle on the basis of a series of histological characters. This seriation has been widely adopted and has greatly facilitated the comparisons between human endometria from different series, since ovarian data are inadequate or lacking. Markee[3] followed the sequence of events in the cycle in living transplants and based his schema[46] on measurements of individual transplants. Since he was observing successive cycles, he could locate events by their *relative* position in a particular cycle, whether it was long or short. He shows 2 significant fluctuations in the endometrium which have been generally overlooked, namely, a slight regression at midcycle and a striking and constant one premenstrually. The premenstrual regression was the most striking change observed by Hoffmann, Ober, and Schmitt[47] in bits of ectopic endometrium in the dorsal vaginal fornix of a woman during 10 successive menstrual cycles.

The following observations on a series of 49 entire uteri of rhesus, seriated on the basis of the ovarian findings, agree with Markee's schema and confirm

the findings by palpation of Hartman.[41] They provide evidence that the mid-cycle regression occurs immediately after ovulation and show striking changes in both endometrium and myometrium before the onset of menstrual extravasation. The thickness of the endometrium and myometrium near the midline of the corpus was measured in thick sections prepared to minimize shrinkage, or on blocks of uterus promptly fixed and preserved in alcohol. The striking differences in uteri from the same phase of the cycle (Fig. 21, upper graphs) were found to be due largely to differences in the size of the uteri. They were compensated for by using the ratio of endometrium to myometrium (Fig. 21, lower graph). The following changes can be recognized:

1. As the endometrium thickens during the repair and early follicular phases, the ratio of endometrium to myometrium gradually approaches unity (Figs. 12 and 13).



Figs. 12 to 20 are photographs of uterine wall cut perpendicular to surface of endometrium showing relative thickness of endometrium and myometrium in *rhesus monkey*. Boundary between them indicated by arrows (see Fig. 21). Figs. 12 to 18 are from injected uteri cut into thick slabs and processed so as to minimize shrinkage.

Fig. 12.—Specimen B329. Transition from menstruation to repair. Day 5 of cycle. Endometrium:myometrium = 0.46 to 1. Little injection mass reached inner myometrium. (480 μ. ×15.)

Fig. 13.—Specimen B302. Follicular phase, day 15 of cycle. Ratio 0.76. Injection complete. (480 μ. ×15.)

Fig. 14.—Specimen B338. Immediately preovulatory stage, first maturation division of ovum in 6.0 mm. Graafian follicle. Day 12 of cycle. Complete injection of a larger uterus than in Figs. 12 and 13. Ratio 0.98. (400 μ. ×15.)

2. When there are large growing follicles, the endometrium is slightly thicker (Fig. 14).

3. In 2 specimens obtained promptly after ovulation, there is histologically a distinct loss of stromal ground substance from the endometrium, which thins out. This corresponds to the observations of Markee at "midcycle" (Fig. 15).

4. In the early progravid, that is, the preimplantation, phase, the ratio returns to unity.

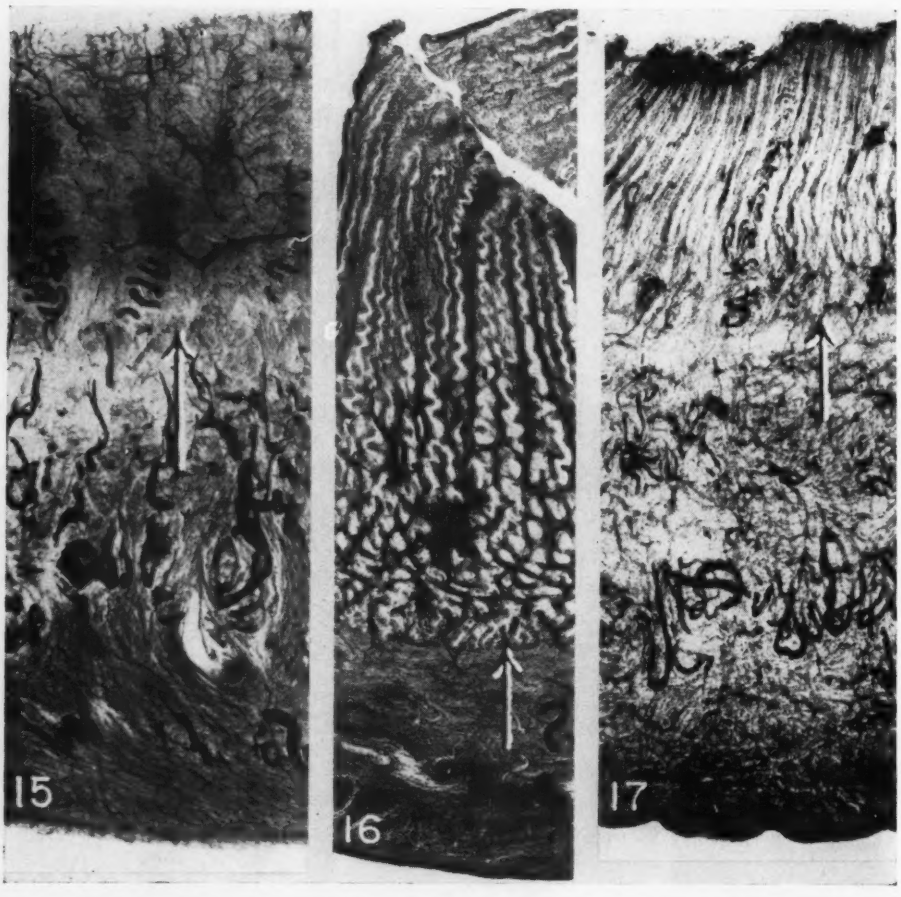


Fig. 15.—Specimen B323. Obtained less than 15 hours after ovulation on day 11 of cycle. Collapsed Graafian follicle; normal ovum in tube. Injection complete despite constrictions in many coiled arteries. Ratio 0.55. (480 μ. ×15.)

Fig. 16. Specimen B316. Late progravid phase. Day 29 of cycle. Relaxation of myometrium maximal. Ratio 2.82. (200 μ. ×15.)

Fig. 17. Specimen B314. Phase of menstruation, day 1. Little loss of tissue; reduction in endometrium due largely to loss of stromal ground substance and secretion.[61] Typical menstrual thickening of myometrium. Ratio 0.54. (480 μ. ×15.)

5. Toward the end of the progravid phase, there is a progressive thinning out of the myometrium as the endometrium thickens, with increase in ground substance and accumulation of secretion (Fig. 16). At the same time, the uterus as a whole has enlarged and softened.[41]

6. Regression in the corpus lutem is associated with a reversal of the progravid relations. The endometrium loses ground substance and secretion, shrinking greatly, while the myometrium thickens. This involution of the endometrium precedes extravasation (Fig. 18). Markee[2] found it the most constant precursor of menstruation.

7. Vascular congestion and extravasation result in a relative thickening of the endometrium as the myometrium thickens (Fig. 19), and the uterus becomes firmer.[41]

8. As a result of sloughing and continued involution, the ratio becomes 1:2. At the end of anovulatory menstruation, it may reach 1:3.

9. During the phase of repair, the ratio rises as stromal ground substance increases (Fig. 12). The broken lines at the right of Fig. 21 indicate 2 transitional stages between menstruation and repair, which are also shown at the left.

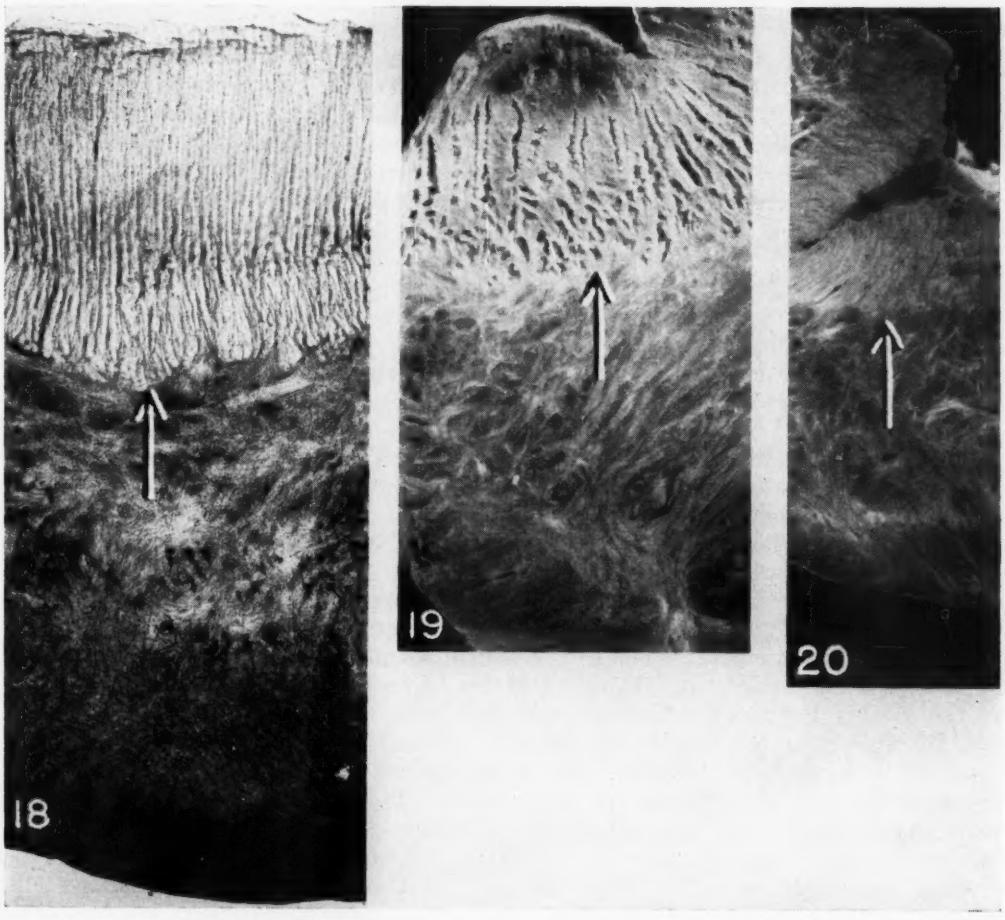


Fig. 18.—Specimen B318. Ischemic phase, day 42. Corpus luteum in early regression. Endometrium involuted, myometrium contracted (compare Fig. 16). Ratio 0.73. (480 μ. ×10.)

Fig. 19.—Specimen C15. Menstrual phase, day 1. Extravasation (dark in figure) preceding shedding. Characteristic collapsed glands of ovulatory cycle. Ratio 0.60. Photograph of cut surface of block in 80 per cent alcohol (compare Fig. 17). (×10.) (Courtesy of G. W. Corner, Sr.)

Fig. 20.—Specimen C128. Transition from menstruation to repair, day 4 of cycle. Involution complete. Uterus small, but ratio (0.46) corresponds to others of this period (see Figs. 12 and 21). Block in 80 per cent alcohol. (×10.) (Courtesy of G. W. Corner, Sr.)

The retarded responses of zone IV to the ovarian hormones can be attributed to the continuous and probably rapid blood flow. In the superficial zones, the flow is not only intermittent, but the venous system is adapted to retarding it, thus facilitating diffusion.[3] Other features of the vascular system have been discussed by Bartelmez.[48] Hollstein,[49] using the fluorescent dye, thiazin red, has presented evidence that the superficial capillaries (?) become permeable, especially to serum albumin.

Suggestions as to the Adaptive Significance of the Distinctive Cyclic Changes in the Uterus.—

Adaptations are fundamental features of all living creatures, and the interpretation of a character as an adaptation can at least serve as a working hypothesis. It has been argued that successful extrauterine pregnancies throw doubt on such interpretations. However, ectopic pregnancies so rarely proceed normally to term that they are negligible in any consideration of the conditions which produce enough young to insure the survival of a species.

The primate endometrium appears to be unique in having the superficial one fourth or more supplied exclusively by vessels, the "coiled arteries,"[24] which are more sensitive than other arteries or than the myometrium to changes in available ovarian hormones. They react characteristically to estrogens and progesterone.[2] Other vascular beds show similar, though normally feebler, reactions during the cycle.[50, 51] Abnormally, however, even bleeding from other mucous membranes may occur as in vicarious menstruation.

So long as there is available estrogen, the capillary bed of the coiled arteries is rhythmically dilated and constricted.[2] It may be suggested that this rhythm is due to minute-by-minute fluctuations in blood estrogen. During the follicular phase, the tone of the uterine muscle and the high amplitude of the progressive rhythmic contractions prevent the accumulation of secretion in the uterine glands, which remain straight and narrow. It will be remembered in this connection that the myometrium has the relations of a muscularis mucosae. Shortly before ovulation, when estrogen reaches a peak, an endometrial hyperemia develops,[2] which can be correlated with the metabolic maxima of the endometrium, as discussed by Reynolds[40] in Part V of *Physiology of the Uterus.* When the maturation divisions of the ovum have appeared (in rhesus), the secretion has become more abundant and dense.[5] Immediately after ovulation, many coiled arteries can be found constricted, the endometrium thins out, and the stroma loses ground substance (compare Figs. 14 and 15). This may serve to augment the activity of the myometrium in the discharge of secretion into the lumen of the uterus thus facilitating insemination. The involution of this period can be correlated with the fall in blood estrogen observed in women at midcycle by Markee and Berg[29] and by Littrell and Tom.[52] The activities of the rhesus Fallopian tubes at this time have been observed by Westman.[53]

By the time the ovum reaches the uterus, progesterone dominance has resulted in important changes. The secretion has become richer in mucin and glycogen, and it accumulates in the glands. This can be directly correlated with the change in uterine contractions, which become localized and reduced in amplitude.[40] By the time the ovum is ready to be implanted, the myometrial relaxation is at its height (Fig. 16), the endometrial circulation has become slower.[3] The coiled arteries have become more complex, and the distention of the myometrium has contorted their afferent radial arteries as well. Such changes contribute to the slowing of the blood flow. The development of edema superficially has not only loosened the stroma but distended the capillary net as well. These changes may well facilitate the spread of the trophoblast. By the time of the next expected menstrual period, there is evidence of a marked reduction in the flow of blood to the endometrium, reducing the danger of a hemorrhage great enough to wash off the ovum, which is only 0.1 mm. in diameter at the time and loosely attached at the surface of the endometrium.[48, 55] To judge from the changes in the nonpregnancy cycle, the ensuing ischemia would serve to injure or kill maternal cells, facilitating their subsequent destruction by the trophoblastic enzymes. Ischemia is followed by an extravasation of blood at the implantation site. In rhesus some blood always reaches the exterior, constituting the placental sign which can usually

be distinguished from menstruation only by its longer duration.[41, 55] At this time gonadotrophin disappears from the urine,[56] and the corpus luteum is transformed into the structure characteristic of pregnancy.[44] This early regression of the corpus luteum in rhesus can be correlated with a more extensive implantation bleeding than usually occurs in Homo. However, 4 normal early human implantation stages have been described which show extravasations in the vicinity of the ovum. They were obtained at about the time of the next expected menstrual period. Brewer[57] described histological conditions in detail which resemble those of early menstruation in a normal 15 to 16 day implantation site. At least one of the underlying coiled arteries had a characteristic constriction. Similar conditions obtain in the Peters ovum and in 2 similar implantation stages described by Hertig and Rock.[58]

These findings substantiate Corner's[59] interpretation of menstruation as an expression of the mechanism for providing the ovum with maternal blood before the establishment of the placental circulation. In the absence of pregnancy, the extensive extravasation can be accounted for by the more rapid regression of the corpus luteum of menstruation and the greater fall in available ovarian hormones. As a result, not only a small group but all the coiled arteries constrict, perhaps for longer periods. The general ischemia throughout corpus and fundus accounts for the injury to the superficial tissues. When arteries open up, the damaged capillary beds give way, and there is an extravasation to which the artery responds sooner or later by constricting, as Markee[3] observed. The continued retardation of the blood flow accounts for the regression during the flow.

The transitions between ovulatory and anovulatory cycles (Hartman[60] staircase phenomenon) clearly indicate cyclic fluctuations in available ovarian hormones, even in the absence of obvious ovarian changes. They indicate that the two kinds of cycles differ only quantitatively, an ovulatory cycle representing optimal conditions in the delicately balanced hormonal system, since a slight but abrupt fall in estrogen is usually followed by extravasation and bleeding. The same fundamental mechanism seems accordingly to be involved in both ovulatory and anovulatory cycles.

Summary

The terms "proliferative" and "secretory" imply certain unsubstantiated deductions.

1. The supposed resemblance between the mucosa which survives menstruation and the basal zone of other phases vanishes when the reticular framework is specifically stained. Two zones, in addition to the basal zone, can be recognized throughout menstruation and during repair (Figs. 1 to 8).

2. The reduction in thickness after the initial menstrual sloughing is due primarily to loss of ground substance from the stroma. The involution is greatest superficially.

3. Mitoses are practically absent from the stroma during repair (Table I). They are uncommon at first in the epithelium and entirely absent in the "basalis." Mitoses in the stroma are not abundant enough in any phase to account for the observed increases in thickness of the endometrium.

4. The outstanding feature of the repair and follicular phases is the increase in stromal ground substance. The glands are not stretched but keep pace with this thickening by cell division.

TABLE II. DATA ON WHICH FIG. 21 IS BASED

SPECIMEN	DAY OF CYCLE	ENDOMETRIUM MAXIMUM	MYOMETRIUM MAXIMUM	RATIO	
B329	5	1.8	4.1	0.41	Previous cycle anovulatory
C128	4 (1)	1.8	3.9	0.46	Previous cycle ovulatory
B334	8 (5)	2.0	3.9	0.51	Previous cycle anovulatory
C12	10 (3)	2.0	4.0	0.50	Previous cycle anovulatory
C125	7 (1)	2.7	4.5	0.60	Previous cycle ovulatory
C192	43	3.0	4.5	0.66	Follicular atresia
C123	15	4.0	4.1	0.975	Follicular atresia
C1	17	2.2	2.8	0.78	No large follicle (juvenile)
C223	28	2.3	3.7	0.62	No large follicle (adult)
C192	43	3.0	4.5	0.666	Follicular atresia
C124	12	4.4	3.5	0.628	Large follicles
C100	13	5.0	5.0	1.00	Large follicles
B338	12	4.0	4.0	1.00	Large follicles
C109	14	5.4	4.5	1.20	Large follicles
B327	11	5.1	4.2	1.21	Large follicles
B319	11	2.9	4.1	0.71	Less than 1 day after ovulation
B323	11	3.0	5.0	0.60	Less than 1 day after ovulation
C2	14	5.2	5.5	0.945	Tubal egg
H291	18	5.15	4.6	1.10	Tubal egg
C5	18	4.5	4.7	0.957	6-7 day corpus luteum
B309	17	4.9	4.2	1.16	6-7 day corpus luteum
B326	35	4.1	3.7	1.10	7 day corpus luteum
C4	18	4.9	5.1	0.96	7-8 day corpus luteum (dense stroma)
B324	23	5.0	4.3	1.16	7-9 day corpus luteum (dense stroma)
C77	22	4.6	4.2	1.10	8-9 day corpus luteum (dense stroma)
B307	26	4.1	4.9	1.20	Corpus aberrans
H431	23-25	4.6	5.4	0.85	9 day corpus luteum 9 day blastocyst
H234	24-25	6.3	5.7	1.10	10-12 day corpus luteum 9 day+ blastocyst
H304	23	6.1	4.5	1.35	9-10 day corpus luteum 9-10 day blastocyst
C219	22	6.6	4.0	1.65	9-10 day corpus luteum 9-10 day blastocyst
C737	20	3.5	2.5	1.40	11 day corpus luteum
B239	23	8.2	3.8	2.16	10-11 day corpus luteum
B325	21	7.0	3.0	2.33	11 day corpus luteum
B330	27	4.7	3.0	1.57	12 day+ corpus luteum
B316	29	6.8	2.4	2.82	12 day+ corpus luteum
B318	42	4.0	5.5	0.73	11-12 day corpus luteum
B317	1	4.7	4.3	1.09	Day 1 menstruation
B317	1	5.0	3.4	1.47	No sloughing as yet
C15	1	3.9	4.9	0.795	
B314	1	2.2	4.1	0.54	Long ischemic phase
C19	1	2.1	3.9	0.538	
C39	1	3.4	2.6	1.31	No sloughing as yet
B122	1	2.9	6.5	0.447	
B136	1	2.0	5.0	0.40	
C38	2-3	2.9	3.9	0.74	
C56	2	2.9	4.4	0.66	
B313	2+	2.3	4.3	0.535	
B121	2	2.8	6.8	0.41	
B15	3	2.0	5.0	0.4	
C90	3	2.2	5.9	0.37	

5. Secretory activity in the preovulatory period has often been demonstrated both histologically (see Fig. 11) and chemically (see p. 944). The myometrium is structurally a "muscularis mucosae"; its characteristic activity in this phase keeps the highly fluid secretion from accumulating in the glands.

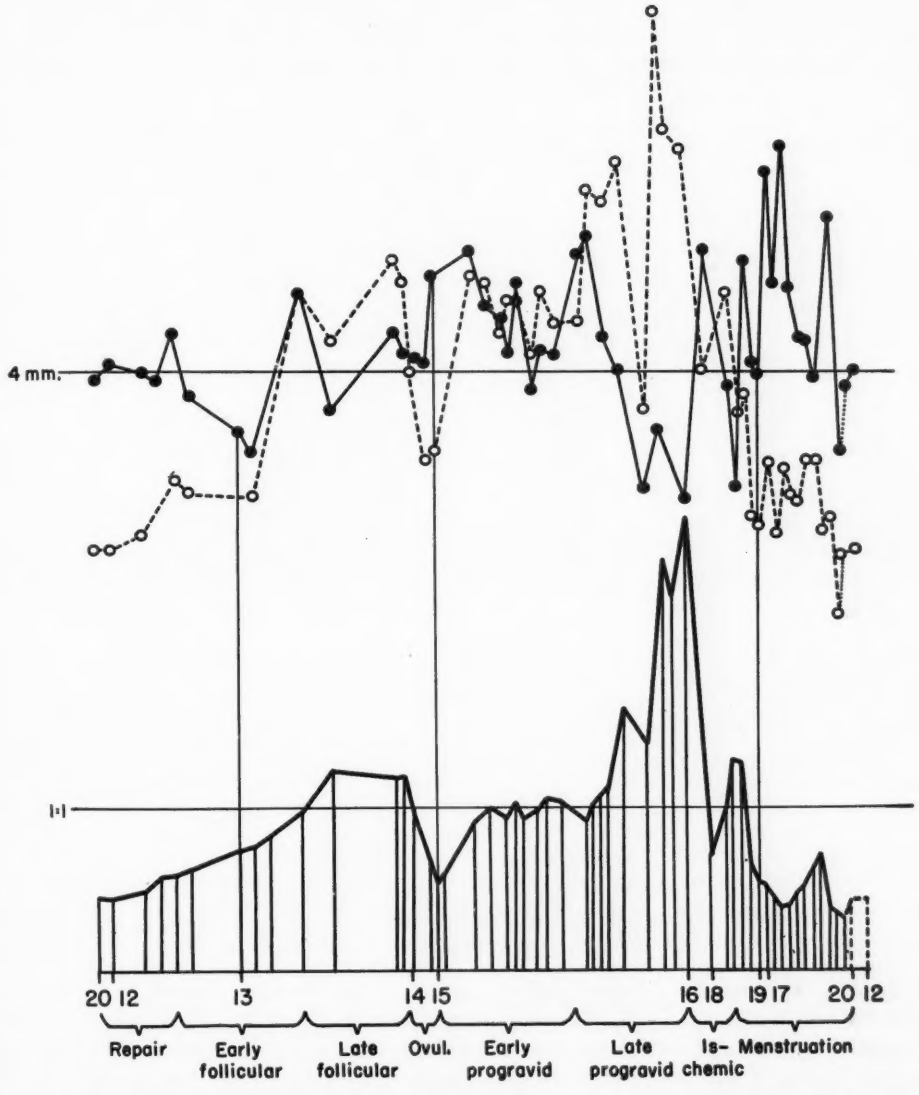


Fig. 21.—Plots of thickness of endometrium and myometrium and of their ratio from 49 rhesus uteri seriated primarily on the basis of ovarian findings. O O indicate measurements of endometrium in midline of corpus. • • indicate corresponding myometrium measurements on thick sections prepared to minimize shrinkage (Figs. 12 to 18) or on blocks of uterine wall measured in 80 per cent alcohol (Figs. 19 and 20). Use of ratio of endometrium to myometrium compensates for differences in absolute size of uteri (compare Figs. 19 and 20 and their ratios). The location of each specimen measured is indicated by vertical lines on the graphs. Those with extensions of broken lines to the upper graphs are illustrated in Figs. 12 to 20. The transitions from menstruation to repair (Figs. 12 and 20) are entered at beginning and end of graphs. The significant regressions can be correlated with loss of stromal ground substance (see text) in phases of ovulation and prehemorrhagic ischemia. They have been overlooked in most diagrams of the cycle. The absence of ovarian data in human series makes the ovulatory regression difficult to demonstrate, but some human endometria from midcycle show denser stroma than in earlier and later stages. This figure visualizes data of Table II.

6. The secretion in the postovulatory period is prominent because of its greater density and the fact that it accumulates in the glands as a result of the change in myometrial activity under progesterone dominance (p. 946).

7. The term "follicular phase," widely used in comparative studies, has no misleading implications and emphasizes the controlling ovarian activity. Since secretion is not confined to one phase of the cycle, the term "progravid" or "progestational" is to be preferred to "secretory," since all of the adaptive features of an endometrium controlled by the corpus luteum are recognized.

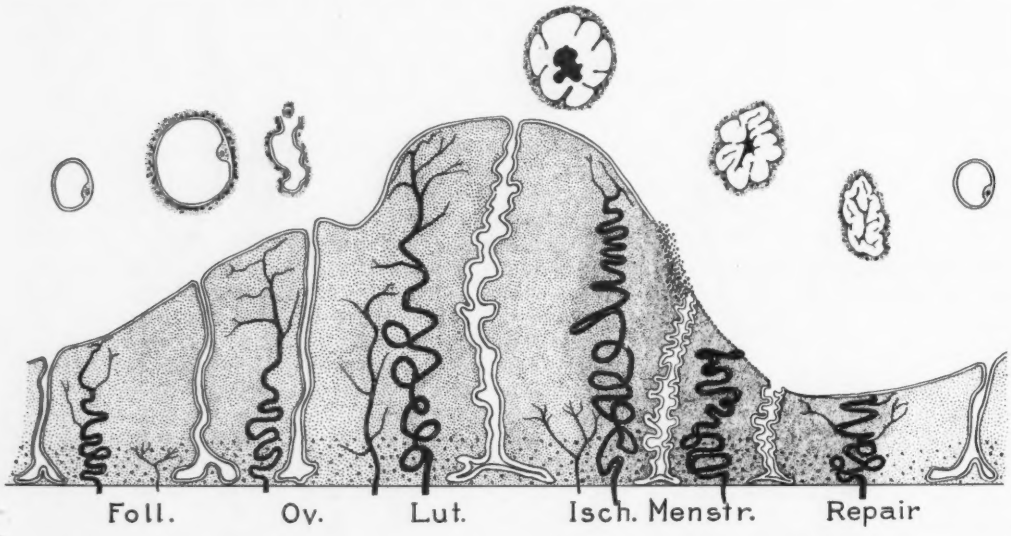


Fig. 22.—A diagram indicating correlated changes in ovary and endometrium during an ovulatory cycle of rhesus monkey. Thickness of mucosa, density of stroma, gland form, and 3 types of arteries are indicated. There is a gradual rise in thickness up to the time of ovulation, and a brief decline followed by development of progravid phase with accumulation of secretion in the glands due to relaxation of myometrium. This is followed by loss of ground substance from the stroma, which is the primary factor in the premenstrual regression of the ischemic phase. This is a prelude to extravasation and shedding. Incidentally, secretion is extruded and glands collapse. There is further regression throughout the phase of menstruation. More than zone IV (coarse stipple) survives menstruation. During repair, thickening of the endometrium is associated with increase in ground substance in the stroma and growth in the glands.

8. The thickness of the endometrium and the myometrium of rhesus can be compared in appropriately prepared material (Figs. 12 to 20). When the variations in the size of the several uteri are compensated for by using the ratio of endometrium to myometrium (Table II), the graph of cyclic changes exhibits two regressions (Fig. 21) which are not represented in diagrams based on general impressions. There is a slight regression immediately after ovulation and a prominent one prior to menstrual extravasation. They are shown in the graph of Markee,[3] which is also based on measurements.

9. Suggestions are made as to the adaptive significance of the various cyclic changes in the endometrium (p. 950).

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TOTAL EXCHANGEABLE SODIUM IN THE MENSTRUAL CYCLE*

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THE purpose of the study was to do serial measurements of total exchangeable body sodium in women throughout the menstrual cycle to determine whether there is a sodium retention during normal menstrual cycles. It is common belief that there are changes in body sodium content in pregnancy, toxemia of pregnancy, the premenstrual tension syndrome,[9] and perhaps also in the normal menstrual cycle. The intent was to establish normal control values and ranges for body sodium content, and to determine the daily pattern of body sodium for possible changes concomitant with the endocrinologic changes of the normal menstrual cycle. Serial measurements of total exchangeable body sodium were made on a daily basis with the use of isotope dilution techniques.

Sodium metabolism can be studied by metabolic balance methods, or, as has been done more recently, by isotope dilution techniques.[4, 16-19] When a known amount of radioactive isotope is administered, it exchanges or is diluted by the naturally occurring element in the body, and the total amount of body element with which the tracer isotope has exchanged or mixed can be calculated by the dilution principle. That is, if the concentration of radioactive isotope is known or measured before and after dilution in the body, the volume or weight of the diluting substance can be calculated.

The basis of the method is the chemical dilution principle that the weight or mass of the diluted solute or tracer substance remains constant before and after dilution, expressed by the formula $C_1V_1 = C_2V_2$, where C and V represent concentration and volume before and after dilution. The method is suitable for volume or "space," and solid or weight studies using either dyes or isotopes, and was first used by Keith, Rowntree, and Geraghty[12] in 1915 for dye studies measuring plasma volume. The method has been popularized in the United States by F. D. Moore and his co-workers.

Dilution studies with the radioactive isotopes are based on observations that the tracer isotopes behave chemically and physically in the body in a manner identical with that of the natural isotopes of an element, except that a proportion of the radioactive atoms will disintegrate with the emission of radiation which can be detected, measured, and recorded.[20]

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Rearranging in the formula $C_1V_1 = C_2V_2$, we have $V_2 = \frac{C_1V_1}{C_2}$ where V_2 is the total weight of the body substance with which the tracer isotope has mixed. The concentration C is the radioactivity per unit weight of the mixture of isotopes of the element to be measured, that is, microcuries of radioactive isotope per milliequivalent of natural element. C_1V_1 is the dose of radioisotope administered; the amount of natural element given with the tracer is so small in comparison to the total body content that it can be ignored. The ratio of radioactive isotope to natural isotope is called specific activity. C_2 is the specific activity of a body sample after equilibrium has been reached, e.g., the number of microcuries of radioactive sodium per milliequivalent of naturally occurring body sodium in any body sample. In determining the sodium content of a sample chemically or photometrically, the radioactive isotope cannot be distinguished from the natural isotope and is also measured. However, the quantity of radioactive isotope is negligible in comparison to the total. Substituting in the formula $V_2 = \frac{C_1V_1}{C_2}$ we have:

$$\text{Total exchangeable element} = \frac{\text{amount of radioactive isotope given minus excretion}}{\frac{\text{radioactive isotope per unit weight or volume body sample}}{\text{natural element per unit weight or volume body sample}}}$$

In most studies it is necessary to measure excretion of the administered radioactive tracer and correct for this loss, in order to know the exact amount of tracer exchanged. However, our method of measuring the isotope remaining in the body, as described below, simplified the technique. By the above formula, when equilibrium of exchange has occurred, the quantity of body element with which the tracer has exchanged is inversely proportional to the radioactive isotope per unit weight of the element in any body sample; or, more simply, total exchangeable element is inversely proportional to the specific activity of any body sample.

$$\text{Total exchangeable element} = \frac{\text{radioactive isotope remaining in the body}}{\text{specific activity of any body sample}}$$

If the radioactive isotopes of sodium exchanged uniformly and completely with the naturally occurring body sodium, the total exchangeable sodium would equal the total sodium content of the body. However, exchange of radiosodium is neither complete nor homogeneous; exchange into cerebrospinal fluid and brain is somewhat slower than elsewhere, and exchange into bone is slow and incomplete.[2, 11, 13, 15] The total exchangeable sodium, however, represents the body content of sodium which is available for exchange with the tracer isotope, and is thought to represent the available or metabolically active sodium in the body.[19]

There is much available information from previous dilution studies with the radioactive isotopes of sodium weights 22 and 24, Na^{22} being an isotope with a long half life of about 2.6 years, Na^{24} an isotope with a short half life of about 15 hours. Equilibrium of tracer sodium and natural sodium would in theory be reached when the specific activity of the body sample for study was equal to the total body specific activity. Extensive studies of the rates of

equilibrium for sodium[22] and sodium[24] have been carried out, and the distribution of radiosodium into various body fluids and tissues determined.[3, 6, 7, 13, 15] There is some difference of opinion regarding the choice of the route of administration of the tracer isotope; Miller and Wilson[15] could detect no significant difference in the value obtained for total exchangeable sodium if the tracer were administered by oral or intravenous route, but Forbes and Perley[7] abandoned the oral route as unsatisfactory. Extrarenal loss of administered radiosodium via bowel and skin is small enough to be disregarded for short-term studies with Na^{24} [8,15] but constitutes a source of error in long-term studies with Na^{22}.[1] Any body sample—tissue or body fluid—could be chosen for an equilibrium sample for measuring specific activity, but of course plasma or urine is chosen in practice.

The difficulties and cost of metabolic balance studies are well known, and serial blood levels of body constituents do not correlate well nor parallel their total body content as determined by other techniques.[19] In practice many isotope dilution studies are cumbersome and time consuming for the laboratory, and a source of discomfort and disturbance to the subject. An isolated measurement here and there is often all that can be practically undertaken. In most studies all urine must be continuously collected to measure loss of tracer isotope; in long-term studies over a month this in itself heartily discourages volunteers. Also, in long-term studies some correction must be determined for extrarenal loss of the isotope. Some isotopes with a short half life have scarcely reached equilibrium before their decay has made their measurement difficult, and studies can be continued only for several hours or days.

The construction of a total body counter and description of an improved method for clinical studies of total exchangeable sodium in this department minimized many of these difficulties and furnished the basis for this study.[21] A total body counter with a Geiger-Müller counter system permits measurement of the tracer dose remaining in the body so that continuous collection of urine for measurement of excretion is unnecessary, after the initial equilibration period. Also, by measuring the tracer remaining, errors due to extrarenal loss are avoided. The isotope Na^{22} with its 2.6 year half life (biological half life about 11 days) permits daily measurement of total exchangeable sodium with a minimum of disturbance to the subject. The combination of total body counter and long half life isotope made it feasible to take serial measurements of body sodium on volunteers.

Method

Normal women volunteers were selected. They included student nurses, laboratory technicians, secretaries, nurses, sisters, and other hospital personnel, between the ages of 16 and 39 years. There were no menstrual complaints except that a few subjects had mild dysmenorrhea. There was no interference with usual routine and no dietary control or restriction. Age, weight, height, and menstrual history were recorded and each subject was asked to record daily basal temperature readings. From 5 to 21 μc of Na^{22} was administered orally to each of the subjects.* As the experiment proceeded it proved easier

*The radioactive Na^{22} was prepared by Dr. J. E. S. Bradley of the Postgraduate Medical School of the University of London, by extraction from a magnesium target irradiated in the University of Birmingham cyclotron. The activity of the dose which was made up with a small amount of sodium chloride as carrier was measured in a calibrated ionization chamber.

to administer the isotope in small divided doses at about 2 week intervals to avoid initially high counting rates and later very low counting rates. The amount of Na^{22} given to the subjects varied considerably; those who excreted sodium rapidly and those who had long menstrual cycles were given the most. The smallest over-all total amount given was 18 μc and the largest 47 μc (five divided doses); the average was 30 μc. The radiation dosage is calculated on the basis of the biological half life which is about 11 days; 30 μc excreted at this rate will give a total radiation dose of about 0.15 r, or 1/10 of that received from the usual chest x-ray. In no case was the initial dose rate more than one-fourth of that recommended by the International Commission on Radiological Protection. Recheck of the subjects in the total body counter 60 to 90 days after the last administration of Na^{22} showed no measurable remaining isotope, confirming that no permanent retention or deposition of isotope had occurred. Urine was collected for the first 6 to 18 hours, and the radioisotope loss measured. The isotope in the urine excreted subtracted from the dose administered gave the number of microcuries remaining in the body. The counting rate of the dose remaining in the body was compared in the total body counter with a known Na^{22} standard and the reduction in counting rate due to absorption of gamma radiation by the subject's body enabled calculation of a calibration figure for the total body counter for each subject, depending on her size and shape.[21]

The technique and reproducibility of the method were established by oral and intravenous dosages and checking specific activity in blood and urine specimens. Initially 24 hours was allowed for exchange to occur before equilibrium specimens were obtained to measure specific activity. In 6 of the first 20 subjects, however, lower values for TES (total exchangeable sodium) were obtained at this initial reading than subsequently, so the initial reading was discarded and it became the practice to take the first specimen on the second day. Either plasma or urine samples may be used to measure the specific activity but in serial measurements on the same subject urine samples avoid the necessity for daily venipuncture. Daily routine in the laboratory for each subject included body weight, emptying the bladder for a urine specimen for measurement of specific activity, and then measurement of total body radiation in the total body counter. Five or six measurements were made each week; secretarial and laboratory personnel were omitted on Sunday and nursing personnel were omitted on their day off. Measurements were made early in the morning after breakfast at the same time each day.

Measurements

Measurements of total body radiation were made in the total body counter and compared with a known Na^{22} standard to obtain counts per minute per microcurie. The total body counter was of a very similar pattern to that described by Veall and associates[21] using 8 Twentieth Century Electronics G26 Pb. counters arranged on a rigid framework.

The counting rate for subject, background, and standard was always taken to 10,000 counts. Using a sample of the administered Na^{22} as a standard for the total body counter and an aliquot part of it for a urine standard eliminated the necessity of correcting for radioactive decay, which amounted to several per cent over the period of the experiment. The sensitivity of the total body counter for Na^{22} was about 660 counts per minute per microcurie. Urine activity was measured in an E.R.D. scintillation counter,[10] with the use of disposable polythene sample holders. The sensitivity of this counter was about 2,000 counts per minute per microcurie per liter for 10 c.c. sample holders and greater than that for larger sample holders which were used if a large specimen was available.

Chemical sodium measurements were made on duplicate dilutions of urine specimens with an Evans Electro-Selenium flame photometer, with external standards. All specimens and standards were stored in polythene bottles to prevent exchange of sodium with the sodium in glassware. After the microcuries of radioactivity remaining in the body, and the microcuries of Na^{22} per milliequivalent of sodium in the urine were determined, total exchangeable sodium was calculated by the formula:

$$\text{TES} = \frac{\text{microcuries of } Na^{22} \text{ in the body}}{\text{microcuries of } Na^{22} \text{ per meq. Na in the urine}}$$

Results

There were 720 estimations of total exchangeable sodium included in this group. Each menstrual cycle was divided into four equal parts and average values obtained for each quartile for the purpose of comparing one portion of the menstrual cycle with another, and for comparing cycles from one subject with those from another. Each quartile is comparable to a week, and quartile and week are used interchangeably throughout the tables and paper. Twenty subjects were studied through a full menstrual cycle, 6 of these were repeated for a second full cycle, and another 7 had the last half of their second menstrual cycles studied. Two subjects had TES measured twice each morning to check reproducibility of results. This gives a total of 35 sets of data covering 26 complete and 7 half menstrual cycles.

TABLE I. QUARTILE AVERAGES OF TOTAL EXCHANGEABLE SODIUM IN MILLIEQUIVALENTS

SUBJECT	QUARTILE AVERAGES				CYCLE AVERAGE	CYCLE TYPE
	1ST	2ND	3RD	4TH		
E. L.	2,508	2,315	2,504	2,335	2,417	0
V. T.	2,300	2,321	2,266	2,339	2,310	0
B. P.	2,164	2,206	2,286	2,187	2,214	0
A. B.	2,102	2,323	2,254	2,337	2,258	0
A. B.	2,654	2,539	2,235	2,419	2,451	0
A. B.	2,652	2,664	2,448	2,590	2,582	0
J. A.	2,474	2,528	2,528	2,640	2,551	0
J. A.	2,737	2,469	2,603	2,573	2,595	0
L. A.	1,818	1,822	1,781	1,853	1,815	A
A. B.	2,013	2,149	2,180	2,097	2,106	?0
A. B.	2,142	2,343	2,212	2,214	2,231	A
G. B.	1,929	1,806	1,904	2,078	1,930	?0
G. B.	2,189	2,167	2,256	2,375	2,260	?0
D. F.	1,910	1,896	1,908	1,974	1,925	0
J. H.	2,033	2,143	2,005	2,273	2,068	0
J. H.	2,171	2,195	2,201	2,152	2,180	?0
Y. J.	2,329	2,220	2,507	2,356	2,352	0
Y. J.		2,402	2,594	2,281	2,462	0
N. J.	1,946	1,988	1,975	1,893	1,948	0
N. J.			2,090	2,025	2,061	?0
J. K.	2,394	2,407	2,294	2,597	2,417	0
J. K.			2,562	2,564	2,563	0
J. K.	2,743	2,298	2,812	2,792	2,633	A
R. M.	2,087	2,054	2,042	1,900	2,016	0
R. M.	2,016		2,121	2,098	2,094	0
C. S.	2,207	2,292	2,296	2,145	2,238	0
C. S.	2,174	2,608	2,272	2,431	2,374	0
I. S.	2,192	2,237	2,254	2,094	2,194	?0
I. S.			2,150	2,495	2,380	?0
D. T.	2,117	2,189	2,066	2,208	2,146	0
J. R.	2,384	2,362	2,342	2,043	2,280	0
J. R.	2,311	2,511	2,363	2,223	2,363	0
M. V.	2,538	2,373	2,464	2,397	2,435	0
M. B.	2,297	2,431	2,344	2,419	2,375	0
M. B.	2,449	2,428	2,584	2,556	2,501	0
Average	2,253	2,269	2,256	2,267	2,261	

Total Exchangeable Sodium.—

The average of all TES determinations throughout the menstrual cycles was 2,261 meq. of total exchangeable sodium (Table I). This is a rather low average figure for exchangeable sodium, but the average weight of our subjects was only 58.3 kilograms (128 pounds). There was a wide range of values for TES. The lowest monthly average was 1,815 meq. (weight of subject 100 pounds), the highest 2,633 meq. There were wide day-to-day fluctuations in TES which would include both dietary changes and experimental errors. The daily measurements of TES were expressed in terms of the monthly average for each individual and standard deviations calculated for each subject. In 15 cycles the average TES for the fourth week exceeded that for the first week, but in only 2 cases was the increase greater than σ and neither exceeded 2 σ. The average TES for the group showed no significant change throughout the four quarters of the menstrual cycle. Table I summarizes the weekly (quartile) TES averages.

In 2 cases in which two daily measurements were taken, the first immediately after breakfast and the second several hours later, the difference in the monthly averages for the two sets of data was found to be 5 per cent. These data are as follows:

SUBJECT		WEEK 1	WEEK 2	WEEK 3	WEEK 4	AVERAGE
A. B.	No. 1	2,654	2,539	2,235	2,419	2,451
	No. 2	2,652	2,664	2,448	2,590	2,582
M. B.	No. 1	2,297	2,431	2,344	2,419	2,375
	No. 2	2,449	2,428	2,584	2,556	2,501

In both cases the average of the second determinations was about 5 per cent above that of the first determinations. However, one might expect a slight increase in TES over this period as breakfast sodium is absorbed. It has been found previously by measurements before and after noon that lunch will lead to an apparent 2½ per cent increase in TES.[21]

In a few instances repeat measurements were made within half an hour and plasma as well as urine samples were used to estimate specific activity.

SUBJECT	TES 1ST MEASUREMENT		TES 2ND MEASUREMENT		TES ONE-HALF HOUR DIFFERENCE
A	Urine	2,225	Urine	2,235	10
B	Urine	2,360	Urine	2,373	13
	Plasma	2,462	Plasma	2,445	17
C	Urine	2,265	Plasma	2,240	25

TES per Kilogram.—

Expressing total exchangeable sodium as milliequivalents per unit of body weight eliminates the factor of body size and allows comparison between subjects. Table II summarizes milliequivalents of total exchangeable sodium per kilogram of body weight. The over-all average value obtained was 39.2 meq. of sodium per kilogram of body weight, a figure which approximates those of other investigators.

Body Weight.—

The average weight of our subjects throughout the study was 58.3 kilograms (128 pounds). Table III summarizes the average weekly weights for each of the subjects. In only 4 cycles was a weight gain between the first and fourth weeks of greater than σ demonstrated and none of these exceeded 2 σ. There was weight loss in other subjects, and the over-all average of the group showed no significant weight change throughout the four quarters of the menstrual cycle.

TABLE II. QUARTILE AVERAGES OF TOTAL EXCHANGEABLE SODIUM IN MILLIEQUIVALENTS PER KILOGRAM

SUBJECT	QUARTILE AVERAGES				CYCLE AVERAGE
	1ST	2ND	3RD	4TH	
E. L.	39.31	36.29	39.07	36.80	37.89
V. T.	36.80	36.93	36.10	37.53	36.90
B. P.	36.08	36.64	37.58	35.94	36.61
A. B.	41.50	45.57	44.11	45.87	44.32
A. B.	51.70	49.74	43.50	47.06	47.86
A. B.	51.84	51.88	47.64	50.24	50.29
J. A.	31.65	31.90	32.43	33.85	32.33
J. A.	35.16	31.72	33.42	32.96	33.32
L. A.	39.51	39.55	38.66	39.96	39.35
A. B.	35.33	38.64	37.72	36.59	36.76
A. B.	37.52	40.91	38.20	38.62	38.87
G. B.	37.70	35.68	37.26	40.19	37.72
G. B.	42.47	41.99	44.94	46.24	44.12
D. F.	35.78	37.39	34.72	36.65	36.19
J. H.	37.11	38.93	36.38	40.66	37.57
J. H.	39.57	40.51	40.22	38.93	39.81
Y. J.	36.24	34.82	38.98	36.64	36.64
Y. J.		37.42	40.61	36.04	38.60
N. J.	35.25	35.96	35.83	34.38	35.31
N. J.			37.46	36.36	36.96
J. K.	37.63	38.20	36.38	40.97	38.20
J. K.			39.88	40.14	40.02
J. K.	43.07	36.24	44.31	43.77	41.41
R. M.	34.78	34.34	34.46	31.85	33.79
R. M.	33.30		35.52	35.04	34.94
C. S.	38.94	40.69	40.85	38.03	39.69
C. S.	39.31	47.38	40.79	43.54	42.67
I. S.	35.12	36.03	36.54	33.51	35.31
I. S.			34.68	39.52	37.90
D. T.	37.51	38.99	36.36	39.00	37.99
J. R.	36.74	35.95	37.02	32.18	35.39
J. R.	35.01	35.50	35.60	33.70	35.58
M. V.	39.90	36.73	37.45	37.00	37.61
M. B.	44.44	47.23	45.72	47.11	46.18
M. B.	47.35	47.15	50.42	49.79	48.61
Average	38.90	39.48	39.05	39.25	39.16

Ovulatory Cycles.—

Basal temperatures were recorded daily by all of the subjects. The cycles were recorded as ovulatory, questionably ovulatory, and anovulatory, and are marked O, A, and ? on Table I. There was no detectable difference in the TES pattern among the ovulatory, questionably ovulatory, and anovulatory cycles.

Urinary Sodium and Potassium.—

There were wide variations among subjects in the sodium and potassium content of the morning urine specimens, and marked daily changes in the same subject. There was the expected correlation of diet and urine content, the subjects with the highest Na and K intake having the highest urinary values. There was no correlation of urinary sodium, urinary potassium, or sodium-potassium ratio with the menstrual cycle.

Eosinophil Counts.—

Daily eosinophil counts were taken on duplicate peripheral blood specimens of 4 subjects who also had daily total exchangeable sodium determinations throughout their menstrual cycles. There was no apparent correlation of eosinophil count with exchangeable sodium content or menstrual date.[22] Because of their complexity, adrenal function and endocrinologic correlative tests with TES are not feasible on a daily basis.

TABLE III. QUARTILE AVERAGES OF BODY WEIGHT IN KILOGRAMS

SUBJECT	QUARTILE AVERAGES 1ST	2ND	3RD	4TH	CYCLE AVERAGE	CYCLE AVERAGE TES/KG.
A. L.	63.90	63.69	64.06	63.72	63.85	37.89
V. T.	62.52	62.85	62.77	62.32	62.59	36.90
B. P.	60.00	60.34	60.85	60.75	60.50	36.61
A. B.	50.66	51.00	51.06	50.89	50.94	44.32
A. B.	51.35	51.27	51.37	51.39	51.35	47.86
A. B.	51.35	51.27	51.37	51.39	51.35	50.29
J. A.	78.15	78.36	77.92	78.00	78.10	32.33
J. A.	77.83	77.86	77.91	78.04	77.90	33.32
L. A.	46.02	46.03	46.38	46.28	46.21	39.35
A. B.	56.98	57.20	57.70	57.16	57.26	36.76
A. B.	57.08	57.26	57.81	57.33	57.38	38.87
G. B.	51.24	50.62	51.07	51.70	51.16	37.72
G. B.	51.54	51.26	50.20	51.40	51.14	44.12
D. F.	53.31	52.43	53.34	53.84	53.26	36.19
J. H.	54.54	55.08	55.10	55.90	54.98	37.57
J. H.	54.85	54.24	54.77	55.28	54.81	39.81
Y. J.	64.28	63.80	63.94	64.30	64.08	36.64
Y. J.		64.20	63.88	63.30	63.77	38.60
N. J.	55.20	55.17	55.12	55.06	55.13	35.31
N. J.			55.75	55.58	55.67	36.96
J. K.	63.52	63.07	63.08	63.35	63.26	38.20
J. K.			64.06	63.85	63.97	40.02
J. K.	63.69	63.40	63.47	63.77	63.56	41.41
R. M.	60.01	59.81	59.28	59.63	59.66	33.79
R. M.	60.06		59.70	59.85	59.91	34.94
C. S.	56.66	56.33	56.24	56.40	56.40	39.69
C. S.	55.30	55.05	55.69	55.83	55.63	42.67
I. S.	62.50	62.08	61.67	62.63	62.23	35.31
I. S.			62.00	63.12	62.75	37.90
D. T.	56.37	56.15	56.81	56.64	56.48	37.99
J. R.	64.88	65.70	63.26	63.70	64.35	35.39
J. R.	66.02	66.99	66.27	65.97	66.37	35.58
M. V.	63.58	64.58	64.83	64.78	64.49	37.61
M. B.	51.71	51.48	51.28	51.35	51.45	46.18
M. B.	51.71	51.48	51.28	51.35	51.45	48.61
Average	58.45	58.29	58.17	58.28	58.29	39.16

Excretion Rate.—

Sodium retention, as well as being measured by an increase in TES, may also be detected by a slowing in the rate of excretion of radiosodium. If the body had a compensatory mechanism whereby the intake of salt was decreased if the rate of excretion slowed, sodium retention might be missed by examination of the TES alone. The daily excretion rate of radiosodium was determined, and it was found that there were wide day-to-day variations, but no pattern which changed with the menstrual cycle. Table IV summarizes the weekly averages of the radiosodium excretion expressed as per cent of remaining radioactivity in the body.

Biologic Half Life.—

The biologic half life of Na^{22}, that is, the length of time for half the administered dose to be excreted, has been found to be about 11 days. In giving small divided doses of Na^{22} we found the biologic half life increased with each dose, the excretory rate apparently slowing progressively with time. This slowing of excretory rate was probably due to delay in the excretion of radiosodium which had exchanged with bone sodium. The rates of exchange of radiosodium into and out of various compartments of the body differ; there is rapid diffusion into the vascular and extravascular compartments and slower exchange into the skeletal compartment. It is apparent then that the specific activity

TABLE IV. QUARTILE AVERAGES OF RADIOACTIVE SODIUM EXCRETION RATE IN PER CENT*

SUBJECT	QUARTILE AVERAGES				CYCLE AVERAGE
	1ST	2ND	3RD	4TH	
E. L.	.075	.039	.062	.059	.058
V. T.	.047	.053	.048	.047	.049
B. P.	.083	.053	.081	.058	.068
A. B.	.044	.063	.043	.077	.057
A. B.	.039	.057	.042	.052	.047
A. B.	.039	.057	.042	.052	.047
J. A.	.069	.074	.069	.057	.067
J. A.	.056	.054	.055	.059	.056
L. A.	.047	.037	.073	.046	.051
A. B.	.061	.049	.052	.073	.059
A. B.	.043	.047	.060	.081	.058
G. B.	.067	.064	.072	.073	.069
G. B.	.068	.054	.060	.064	.062
D. F.	.087	.111	.104	.084	.096
J. H.	.044	.062	.053		.053
J. H.	.042	.053	.047	.053	.049
Y. J.	.069	.058	.043	.058	.057
Y. J.		.061	.042	.070	.052
N. J.	.045	.046	.044	.050	.046
N. J.			.027	.053	.040
J. K.	.074	.049	.064	.049	.058
J. K.			.057	.069	.061
J. K.	.062	.068	.036	.080	.060
R. M.	.049	.059	.077	.076	.065
R. M.	.086		.044	.050	.053
C. S.	.082	.058	.057	.062	.064
C. S.		.062	.072	.062	.062
I. S.	.079	.058	.044	.077	.063
I. S.			.153	.047	.071
D. T.	.054	.064	.078	.070	.065
J. R.	.063	.068	.091	.079	.069
J. R.	.072	.060	.056	.056	.059
M. V.	.052	.051	.066	.027	.049
M. G.	.050	.057	.054	.039	.051
M. G.	.050	.057	.054	.039	.051
Average	.060	.058	.059	.061	.060

*Expressed as percentage of the remaining radioactive isotope in the body.

of each of various body compartments is not quite equal to that of the others, nor to that of the body as a whole; and sampling of one of the body compartments may not give a true picture. That is, after a time, the number of microcuries of radiosodium per milliequivalent of natural sodium is higher in bone than in plasma, extracellular fluid, or urine, where there is no delay in excretion. Thus, in measuring the specific activity in plasma or urine samples under such conditions the specific activity of these samples is lower than that of bone, and the resulting TES is too high. Measuring specific activity in bone by means of a bone biopsy at this stage would give a high specific activity and the resulting TES would be too low. Theoretically, there is a given point in time for each body component when the specific activity of that sample will equal the specific activity of the body as a whole, depending on the rate of exchange of radiosodium into each given fluid or tissue. Previous workers[5, 7, 14, 15, 23] have given varying estimates of the rate and completeness of exchange between radiosodium and bone sodium and speculated regarding the intra- and extracellular position of bone sodium.[11, 13, 16, 19]

The average half life for the subjects for the first dose was 10.6 days, second dose 11.4 days; and for the small number of subjects in whom the tests were continued, the half life for the third dose was 11.5 days, and fourth dose 12 days. This increase in half life gave rise to an apparent small but steady increase in the figure for total exchangeable sodium. The following averages of TES in succeeding mentrual cycles indicate this increase.

	A. B.	J. A.	A. B.	G. B.	J. H.	Y. J.	N. J.	J. K.	R. M.	C. S.	I. S.	J. R.	AVERAGE
1st cycle	2,258	2,531	2,106	1,930	2,068	2,352	1,948	2,417	2,016	2,238	2,194	2,280	2,194
2nd cycle	2,516	2,595	2,231	2,260	2,180	2,462	2,061	2,563	2,094	2,374	2,380	2,363	2,340
3rd cycle								2,633					

In all cases studied the average of each succeeding cycle exceeded that of the previous cycle. If an experiment were designed to administer the isotope always on the first day of the menstrual cycle it would appear as though TES were gradually rising and sodium retention occurring. However, by continuing our studies on all subjects beyond the first day of the menstrual cycle, we demonstrated that TES failed to fall with menstruation. Consequently the apparent TES rise with time was the result of different specific activities of various body compartments as previously discussed.

Accuracy and Errors

Statistical Errors.—The purely statistical variations due to the randomness of the decay process of radioactivity may be estimated mathematically. The standard error of a 10,000 count measurement is 1 per cent. The background count for the total body counter was about 2,400 counts per minute and the counting rate for the subjects ranged from 7 times background to 1.5 times background. Thus the standard deviation of the counting rate due to the subject alone ranged from 1.2 to 3.6 per cent. That of the Na^{22} standard was 1.3 per cent. The standard deviation of the calculated value of the dose left in the body was between 1.8 and 3.8 per cent. By a similar calculation, the standard deviation of the activity per milliliter of the urine samples was found to lie between 1.4 and 3.0 per cent.

Flame Photometry.—The same pipettes were used for all urine samples, so that any error due to the inaccuracy of the pipettes will be the same throughout the experiment. Operator's errors were minimized by making duplicate dilutions of all samples. The magnitude of possible error in flame photometry depends on the sodium concentration; by keeping the concentration within the maximal sensitivity range of the photometer by proper redilution of samples, errors were reduced.

Other Sources of Inaccuracy.—The samples of urine and of standard for the liquid counter were measured out with the same 10 c.c. pipettes, and the personal errors involved in this operation are assumed to be negligible. Repeated measurements of the same person in the total body counter to estimate the effect of change of stance, movement, etc., usually gave readings within the standard deviation, as the sensitivity of the counter is constant over a large volume.[21] The sensitivity of the counter was calculated for each subject, and there may be small errors which are constant throughout the experiment due to incomplete urine collection during the equilibration period. This will not affect the findings, except possibly to introduce a small percentage error into the actual figure for average TES for the group.

Total Standard Deviation.—Assuming all the above sources of error to have a Gaussian distribution, the total standard deviation for the set of measurements is found to be 3.6 per cent. The standard deviation of all the measurements was just over 7 per cent, showing that day-to-day variations in TES figures reflected a real change as well as experimental errors.

Comment

Our experience with daily TES studies on a fairly large control group, and repeated studies on the same day on some subjects, emphasizes the dynamic status of sodium and water metabolism in the normal subject.

Examination of the data of repeated measurements on the same day shows that the value for TES is immediately reproducible, but that the value changes

in a short period of time, or with sodium or fluid intake, or with urinary excretion. This gives rise to a wide range of normal values in the same subject, and wide variation from subject to subject. Therefore, isolated single measurements of total exchangeable sodium may not be significant. The range may be influenced by such factors as pathologic state, dietary or fluid intake, interval between sodium ingestion and sample, source of sample or experimental error. An additional variation may be due to the "skimming"[3] effect of the kidneys if urine is the sample.

The isotope dilution technique of TES employed here is useful in the study of body physiology because of the ease of serial determinations and because factors such as intake and output are controllable or measurable.

The method is sensitive enough to detect sodium ingestion at a meal and quickly detects sodium loss with mild diarrhea.

When the daily TES values of Table I are examined, it is necessary to keep in mind that arranging the values in sequence for the menstrual cycle often breaks the chronological order of the measurements so that the daily values may at some point actually be one menstrual cycle apart.

There was a tendency toward an inverse relation of body weight and TES per kilogram (Table III) but there were numerous exceptions.

Repetition of measurements for a second cycle in those subjects who appeared to show sodium retention during the first serial determinations failed to confirm such a tendency as a recurring or predictable pattern.

If sodium retention were to occur, it would be evident in TES per kilogram or in the sodium excretion rate. Although in subjects with premenstrual complaints, weight gain is a frequent symptom, our data on subjects without complaints showed no significant weight gain and no sodium retention during the menstrual cycle.

The data presented were the initial study to establish controls and ranges for exchangeable sodium for a series of studies now in progress on total exchangeable body sodium and potassium and total body water in normal and abnormal menstrual cycles, and in normal and abnormal pregnancy and toxemia of pregnancy.

Summary and Conclusions

We have described the theory and technique of an isotope dilution study of serial measurements of total exchangeable body sodium throughout the menstrual cycle; and have presented data on 20 normal subjects from 33 partial or complete menstrual cycles. The study has demonstrated the practicality of daily serial measurements of exchangeable sodium for large groups by use of the total body counter, and it has confirmed that with the technique described there is no permanent deposition or retention of isotope.

The various tables indicate average values and ranges for total exchangeable sodium through the menstrual cycle in the normal subject.

In summary, the study indicated that throughout the menstrual cycles of the normal subjects studied:

1. There is no correlation of TES with urinary sodium, potassium, or sodium-potassium ratio.

2. There is no correlation of urinary sodium, potassium, or sodium-potassium ratio with the menstrual cycle.

3. There is a wide range of TES and TES per kilogram among individuals at corresponding dates of the menstrual cycle, indicating that an extensive series of measurements is necessary to establish normal values and ranges.

4. There is a wide range of TES and TES per kilogram in each subject, indicating the need for serial determinations to establish normal values and ranges.

5. There is no correlation of eosinophil count with TES.

6. There is no correlation of eosinophil count with the menstrual cycle.

7. There is no correlation of TES with ovulatory or anovulatory menstrual cycles.

8. There is no correlation of TES with the menstrual cycle.

9. There is no correlation of TES per kilogram with the menstrual cycle.

10. There is no correlation of excretory rate of sodium with the menstrual cycle.

In conclusion, there is no evidence of cyclic changes in sodium balance or sodium retention in the normal menstrual cycle.

We should like to acknowledge the advice and aid of Professor J. C. McClure Browne, Head of the Department of the Institute of Obstetrics and Gynaecology at Hammersmith Hospital, and of Mr. Norman Veall, Honorary Consultant Physicist to the Institute.

Our grateful thanks are due to all the volunteers who cooperated in this study.

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A CRITICAL ASSESSMENT OF THE VALUE OF X-RAY THERAPY IN PRIMARY OVARIAN CARCINOMA

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DURING our detailed review of primary ovarian carcinoma at the Royal Victoria Hospital,[2] we became extremely interested in the subject of postoperative x-ray therapy. Sober reflection on this subject posed many questions regarding this therapeutic aid; this paper is the product of these thoughts.

It is our opinion that any form of treatment which is distressing to the patient—and even potentially dangerous—must prove its value beyond reasonable doubt. To paraphrase a truism, it is not unwarranted to demand that therapy should not be worse than its omission or the disease itself. This is fundamentally the problem with respect to the use of irradiation therapy in cases of primary carcinoma of the ovary. Every practitioner will agree with us in stating that x-ray is not without its hazards; every physician has been confronted, in addition, with cases of very distressing radiation sickness. For these reasons, it is necessary to establish that combined surgery plus postoperative irradiation is not merely the equal of surgery alone, but is definitely superior to it in the treatment of ovarian carcinoma. We believe that the concept of using something because it does no harm is fallacious. The negative approach is insufficient. X-ray must be shown to be good.

In an effort to help assess the value of x-ray therapy we have carefully analyzed our cases. This analysis forms the basis of this paper.

Material

Our selection of cases has previously been detailed.[2] We are using the same cases for this report with emphasis on the results of radiation therapy. During the period of study, January, 1930 to June, 1950, we had 202 cases which satisfied the criteria of selection, and which, in addition, were seen early enough that 5 years had elapsed before analysis. Of these 202 cases, one was lost after 37 months follow-up and is considered dead at this date. Two others were not followed subsequent to discharge from the hospital and were considered as dead at the date of discharge. This gives us a 5 year follow-up in 98.5 per cent of the cases. Furthermore, 2 other patients were not operated on following admission because of their terminal condition; they died within 30 days, and autopsies were performed. These are included in the over-all survival statistics but are omitted from other comparative statistics.

Review of Series

Clinical Staging.—The rationale for our clinical classification has been previously presented. We will restate the classification since it is basic to further analysis.

Stage 0 Carcinoma in situ with no invasion of the stroma.

Stage I Grossly malignant but confined to the ovary. It can be either solid or cystic with no excrescences or infiltrated adhesions.

Stage II Breakthrough of the ovarian capsule; excrescences, infiltrated adhesions, ruptured capsule (before or at operation). No manifest spread beyond the ovary.

Stage IIA Bilateral ovarian involvement without evidence of any other pelvic metastases.

Stage III Pelvic dissemination: tubes, uterus, other ovary, bladder, rectum, rectosigmoid, pelvic peritoneum.

Stage IV Metastases beyond pelvis.

Stage IVL Liver involvement.

Type of Surgery.—Of the 202 cases, merely a laparotomy was performed in 22.3 per cent because of the advanced nature of the disease. Unilateral removal of the adnexa with or without hysterectomy was performed in 22.7 per cent of the cases, while bilateral salpingo-oophorectomy with or without hysterectomy was performed in 52.4 per cent. In some of the cases of unilateral salpingo-oophorectomy this was merely palliative with the aim only of preventing symptoms of obstruction, etc., from a large cyst. Of the 73 cases of hysterectomy, a total hysterectomy was performed in 26 per cent.

X-ray Therapy.—Postoperative x-ray therapy was utilized in 56 of the 202 cases, an incidence of 27.7 per cent. In the majority of cases, this was given immediately after operation, while in some it was withheld until deemed necessary. A few received more than one course of x-ray therapy. Many of the patients who underwent operation only might have been given irradiation, but they were too ill to receive it.

The cases have been divided into 2 periods: 1930 to 1938 and 1939 to 1950. Our rationale for this is that after 1938 refinements in techniques of roentgen therapy provided the patients with potentially superior treatment. To show x-ray in its best light, such division is mandatory. Postoperative irradiation was given to 30.3 per cent in 1930 to 1938, to 26.5 per cent in 1939 to 1950.

X-ray Technique.—The actual deep x-ray therapy has varied considerably during the period under study. This was of course dictated by the fact that this was a period of evolution both in the quality of therapy units and in the methods of their application. We may say that our techniques have improved steadily since 1930, and in general were in keeping with the techniques used elsewhere at any particular time during this period.

At the present time, our deep x-ray therapy is directed at the abdominal cavity up to the level of the third lumbar vertebra as well as at the pelvic cavity. Opposed anterior and posterior 10 by 25 cm. fields are used with a narrow gap in the midline. Treatment is given daily for 5 days per week for a total of 50 to 60 treatment days. Factors are 220 kv., half-value layer 1.0 mm. cu., and focal skin distance 50 cm. With this technique an estimated depth or

tumor dose of 3,000 r is given in the average case—the skin dose of each port being in the region of 4,500 to 5,000 r. Variations of this technique are occasionally used according to the clinical dictates of the case.

Clinical Stages and Treatment.—In Figs. 1 and 2 an analysis of treatment by stages is depicted. Note that surgery by itself is more common in the early and late stages, while postoperative x-ray combined with surgery is more common in Stages IIA and III. Again, to emphasize a point, the weighting of cases in Stages IV and IVL in the category "Surgery only" is the result of the fact that many patients were too ill to receive x-ray, or died before such treatment could be contemplated.

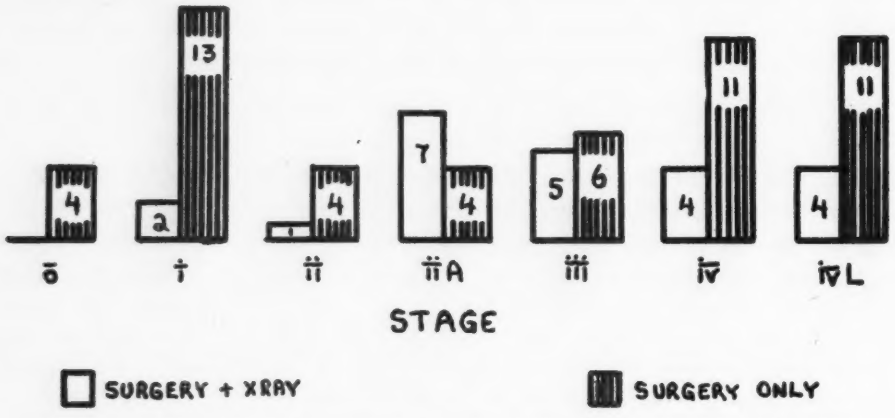

Fig. 1.—Clinical stages correlated with treatment, 1930 to 1938 (76 cases).

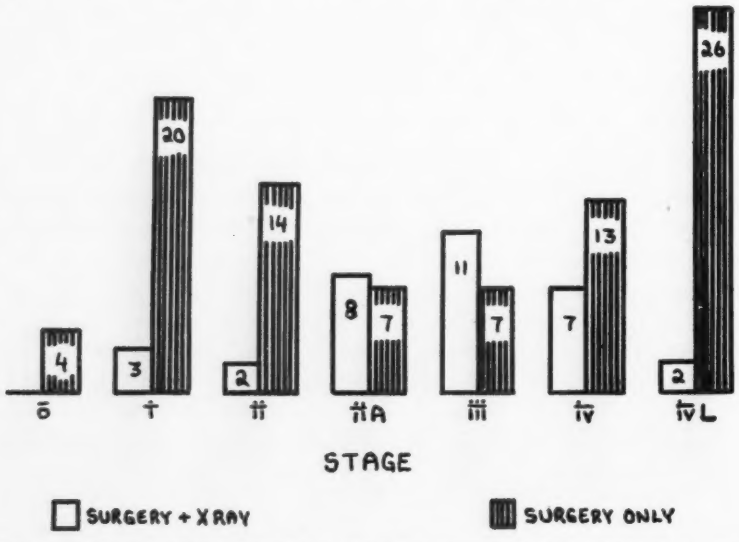

Fig. 2.—Clinical stages correlated with treatment, 1939 to 1950 (124 cases).

Results of Treatment.—Table I summarizes our survival rates.

It is to be noted that our over-all 5 year survival of 37.6 per cent compares favorably with other rates found in the literature and previously reported,[2] which vary from 14.5 to 37.9 per cent. A more detailed analysis shows that survival rates, 5 and 10 year, are higher with surgery alone and that patients who received combined surgery and postoperative x-ray from 1930 to 1938 showed a very poor survival. Possible reasons for this will follow.

We then wondered whether x-ray therapy in cases of carcinoma disseminated beyond the confines of the ovary would show a better prognosis than surgery alone. Table II summarizes our results in Stages IIA, III, and IV. Stage IVL has been purposely omitted for two reasons: first, the cases are weighted unfairly against surgery; second, numerous postoperative deaths may cloud the issue. In this Table, no allowance was made for postoperative deaths; only the 2 cases in which autopsy was performed were excluded. It is obvious that the 5 year survival with surgery is slightly better than that with surgery and x-ray combined, but the difference is not very significant. Stages III and IV appear to offer a slightly better prognosis if postoperative x-ray is given, but again the difference is not appreciable and could be wiped out and possibly reversed if comparable groups were obtained by discarding all postoperative deaths.

TABLE I. OVER-ALL SURVIVAL RATES AND COMPARISON OF RESULTS FROM SURGERY AND SURGERY PLUS X-RAY, 1930-1938, AND 1939-1950.

TREATMENT	NO. OF CASES	DEAD	SURVIVAL			
			5 YEAR	10 YEAR	% 5 YEAR	% 10 YEAR
1930-1938.—						
Surgery only	54	33	20	16	37.7	30.2
Surgery + x-ray	23	18	5	3	21.7	13.0
1939-1950.—						
Surgery only	92	53	38	18	41.8	36.0*
Surgery + x-ray	33	21	12	2	36.4	15.5*

*Based on years 1939 to 1945: surgery only, 50 cases; surgery and x-ray, 13 cases.

TABLE II. CLINICAL STAGES IIA, III, AND IV CORRELATED WITH TREATMENT AND PROGNOSIS

	STAGE IIA		STAGE III		STAGE IV		TOTAL	
	SURGERY ONLY	SURGERY + X-RAY	SURGERY ONLY	SURGERY + X-RAY	SURGERY ONLY	SURGERY + X-RAY	SURGERY ONLY	SURGERY + X-RAY
Dead	3	10	10	12	22	10	35	32
5 year survival	8	5	3	4	2	1	13	10
% 5 year survival	72.7	33.3	23.1	25.0	8.3	9.1	27.1	23.8

Figs. 3 to 6 show in more detail how long the patients survived with and without x-ray therapy. The graphs demonstrate that the patients who received x-ray appear to show a greater prolongation of life up to 18 months and then a dropping off in length of survival. An interesting factor is that the curves are superimposable for 1930 to 1938 and 1939 to 1950. To make the groups comparable, however, all patients who died within one month of admission were excluded (Figs. 4 and 6). Now it is obvious that the early life-prolonging effect of x-ray is not significant and that ultimate 5 year survival is relatively poorer with irradiation.

Review of the Literature

We feel it is instructive to review some of the more prominent articles written on the subject of postoperative irradiation for carcinoma of the ovary. Most of the series are not completely comparable since they contain tumor types (for example, granulosa-cell tumors) not included in our series. Some of these (for example, dysgerminomas) are beyond doubt radiosensitive. Here we will attempt to evaluate the conclusions drawn in each paper in the light of the statistics presented. It is our impression that many have concluded things not substantiated by their results; this is unfortunate for it only perpetuates facts for which valid proof is not present.

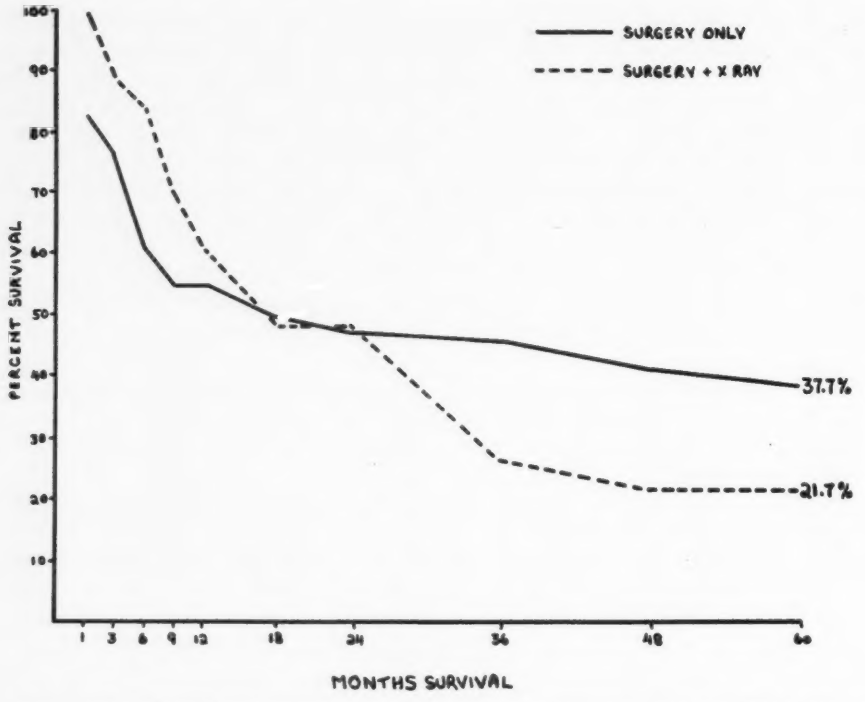

Fig. 3.—Per cent survival by months correlated with treatment, 1930 to 1938 (all stages).

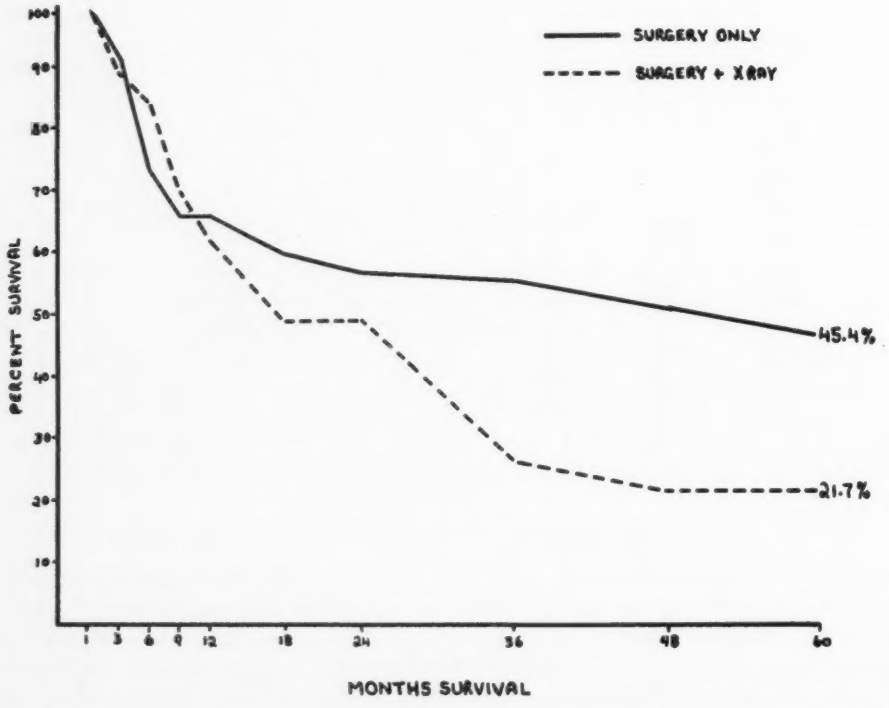

Fig. 4.—Per cent survival by months correlated with treatment, 1930 to 1938 (all stages). All deaths within 30 days of admission excluded.

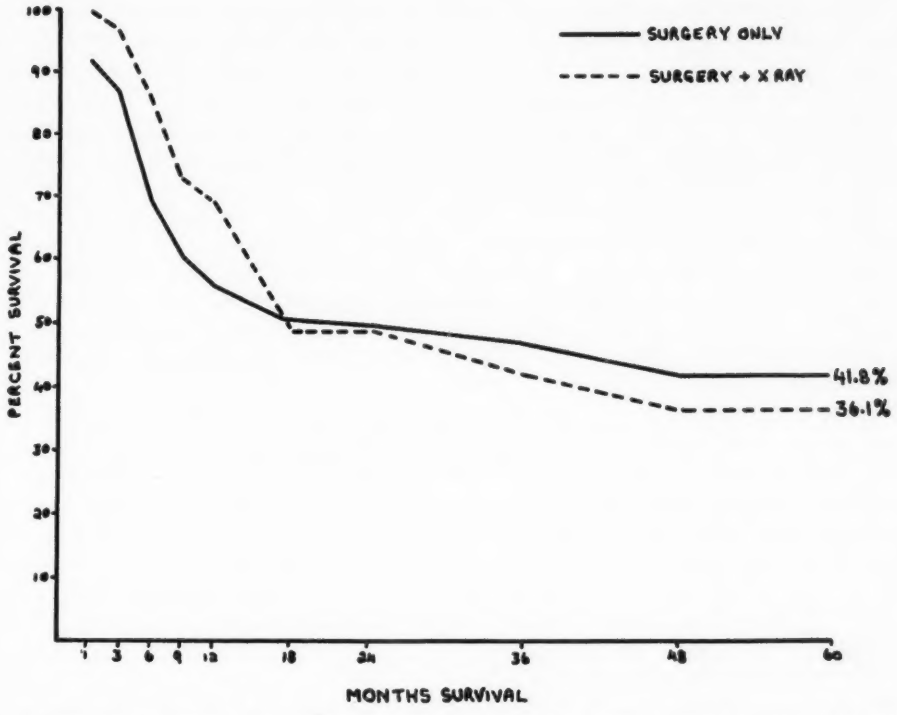

Fig. 5.—Per cent survival by months correlated with treatment, 1939 to 1950 (all stages).

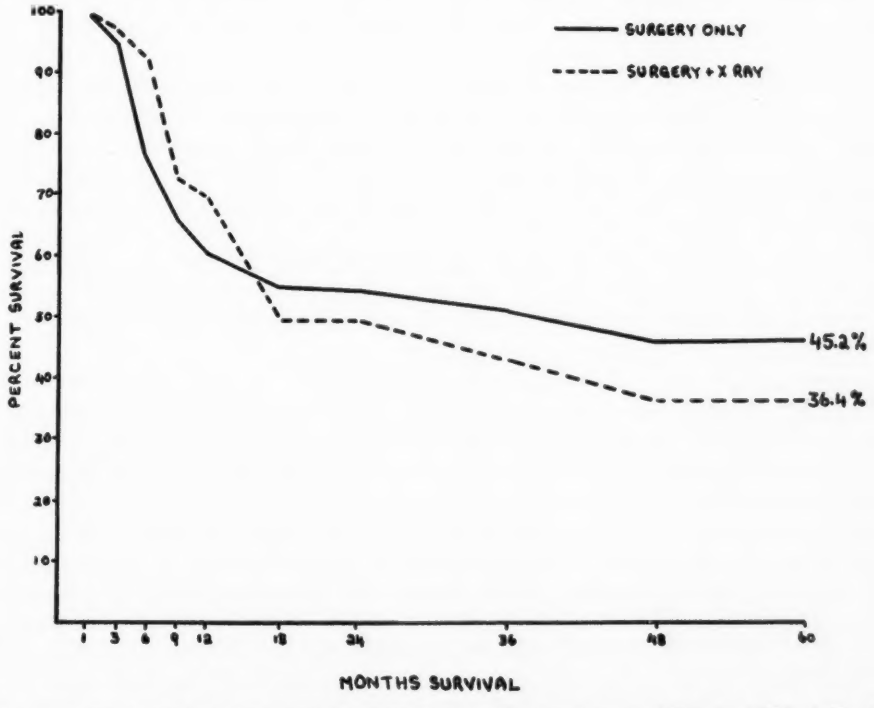

Fig. 6.—Per cent survival by months correlated with treatment, 1939 to 1950 (all stages). All deaths within 30 days of admission excluded.

Meigs[9] holds that x-ray is valuable, but not curative; and that it should be used with peritoneal extensions, spill of cyst fluid, and incomplete surgery. His statistics fail to substantiate his conclusions, however, since they are indicative that surgery alone yields comparable, in fact superior, results.

Munnell and Taylor[11] state that x-ray is of only questionable value when the disease is confined to one or both ovaries; but with dissemination it increases survival, is palliative, and occasionally curative. Unfortunately, their charts of survival time give no indication of how many cases are in each clinical stage treated by either surgery or combined surgery and x-ray. The curves of survival time suggest the value of postoperative irradiation but we have no idea how comparable the cases in each group are. In addition, their series includes 3 dysgerminomas known to be radiosensitive and in 12 cases only a clinical diagnosis was made. The difficulties inherent in pure clinical diagnosis do not need to be re-emphasized.

Taylor and Greeley,[14] whose series included 18 special tumors and 4 benign tumors, show survival curves best for their "adequate" x-ray group, and poorest for the "incomplete" x-ray group. Why the latter should show survival rates lower than surgery alone they fail to explain. It is our impression that their cases were inadvertantly weighted against surgery. However, in the proper perspective, they point out that all but 2 of the radiation cures were in cases in which cure frequently results from surgery alone. Also, survival curves after the first 3 months for surgery alone and surgery plus x-ray are the same. They conclude that the effect of x-ray on the 5 year cure rate and survival curves is less than has been frequently claimed.

Montgomery[10] believes that x-ray should be used on all patients whose general condition warrants it, except those with metastases in the upper abdomen. The exclusion of the latter weights his statistics against surgery; his groups are far from comparable with too few for adequate comparison. In addition, his series includes the special tumors.

Harris and Payne[4] suggested that x-ray aids in prolonging life and relieving symptoms. The latter part of his statement is made in spite of the fact that 40 per cent of their patients had severe radiation sickness. Surely it is of no value to substitute one set of distressing symptoms for another. In addition, their conclusions are based on too small a series, often less than 10 cases in a group, sometimes only one case.

Kerr and Elkins[7] stated that x-ray should always be given to any case where spread beyond the ovary is present. Their results are far from encouraging even with x-ray and notwithstanding the fact that at least 9 benign tumors are included.

Lynch[8] stated that "the profession erroneously credits many cures . . . to x-ray. . . . At least as many carcinomas did not respond at all. . . ." He believed that x-ray is much less important than proper and adequate surgery. All his patients received postoperative irradiation, so no comparison with surgery alone was possible.

Helsel[5] concluded on the basis of his series that radiation prolongs life substantially, often increases comfort, and improves the psychological state. We cannot contest the latter two observations, but his cases far from bear out the primary conclusion, for his selection is definitely to the disadvantage of surgery, with 97 per cent of the cases in the latter group inoperable as opposed to 57 per cent for x-ray.

Walter, Bachman, and Harris[15] asserted that their results established that x-ray arrests the disease and prolongs life; and that where the carcinoma has extended beyond the ovary, surgery is inadequate. Again, the surgery group suffered by case selection, with 41 cases of advanced inoperable disease as

opposed to 13 in the x-ray group. Furthermore, at best, their results are no better than those in other series, even though they show a smaller percentage of the most advanced cases.

Pearse and Behrman[12] stated that total hysterectomy with bilateral salpingo-oophorectomy combined with postoperative x-ray offers the best chance for survival. However, surgery alone was not performed in more than a small fraction of their cases; and their conclusions regarding its value are made on very shaky statistical grounds.

Allan and Hertig[1] concluded that x-ray increases longevity and comfort but does not necessarily cure the disease. Their well-documented statistics support this opinion with x-ray producing a 5 year and 10 year survival significantly better than that of surgery alone. However, their results were not superior to the results in our series by surgery alone (if we use a comparable group).

There are other articles[5, 6, 13] of a similar nature, showing comparable results and the same type of conclusions, but space does not permit their review.

Evaluation of the Literature

We are fully cognizant of the dangers inherent in criticism. But we firmly believe that the only way one can evaluate the claims and counterclaims intelligently is by critical analysis of the assertions. Let it be said that no man's results are on trial; only his conclusions require scrutiny.

Valid conclusions must bear the stamp of statistical corroboration. To conclude something scientifically without the latter is not only poor in theory, but it carries the danger of perpetuating a possibly wrong impression. The literature on carcinoma of the ovary bears witness to this.

In the first place, no attempt is made in many of the series to select the cases properly: secondary tumors are included, as well as special tumors, etc. It is difficult to assess with any degree of confidence any method of therapy in such a potpourri of cases.

Second, many series have either only a few cases treated by surgery only or else none. In either event, no conclusion can be made regarding a comparison of methods of treatment when only one method is adequately covered, yet this occurred repeatedly.

Third, impressions are often given as much credence as facts. Not only the impressions of the authors, but the opinions of other authors, often incompletely validated and open to criticism.

Evaluation of Royal Victoria Hospital Cases

We believe that our selection of cases allows adequate conclusions to be drawn. We further believe that our results will stand the test of statistical analysis in the light of our conclusions. It was our desire to escape all the pitfalls we have pointed out in the papers which preceded ours.

Our results clearly indicate a few important things. The extremely poor survival rate for the cases from 1930 to 1938 treated by the combination of surgery and x-ray suggests that irradiation not only failed to help these patients, but that it may have been actually deleterious.

It is consistently shown in our results that surgery alone gave results at least as good as surgery plus irradiation, and, as a matter of fact, better. As we have previously stated, x-ray must show its value conclusively. It must not merely be as good; it must be demonstrably superior if it is to replace surgery and it must improve the prognosis if it is to follow surgery. This is not the case here.

As for the belief that x-ray therapy has a palliative effect in prolonging life, our charts of survival time fail to substantiate this. In fact, if all truly

postoperative deaths had been excluded, x-ray would show even poorer results than it does. Another aspect of this palliation problem is the alleviation of symptoms. But can we overlook radiation sickness, or the many patients who are not truly suffering from radiation sickness but still show directly related distressing symptoms?

The unpredictability of the course of the disease makes it difficult to evaluate irradiation completely. We have in mind the case of a patient with a Stage IV anaplastic serous adenocarcinoma who lived 13 years following laparotomy and biopsy with numerous subsequent paracenteses. She did not receive x-ray. At postmortem she showed extensive abdominal metastases similar to the state at her original operation. If she had been irradiated she would have been considered a case in point demonstrating the value of radiation therapy.

It was interesting that even in the stages where x-ray should be of most value, i.e., Stages IIA, III, and IV, it failed to establish its importance.

Finally, our results with surgery alone are at least as good as, if not superior to, other results reported in the literature for combined surgery and x-ray.

Conclusions

It is our belief that the value of x-ray therapy as a therapeutic aid in primary carcinoma of the ovary should be critically questioned. This form of treatment is not without its dangers. To retain it one should be able to demonstrate its utility on a sound statistical basis. An assessment of the literature fails to allow such a conclusion. Our own results almost emphatically deny its positive value.

We believe, therefore, for the many reasons given, that x-ray therapy has failed to prove its value in this disease and its use should be at least greatly curtailed.

It is unfortunate that the literature has spawned an opinion which cannot stand the test of statistical evaluation, for this impression has been carried down without critical analysis. The odd spectacular cure in no way supports this over-all impression, for such cases can be found among patients treated with surgery alone.

Perhaps the gynecologist has permitted himself to be influenced too much by the claims of the radiotherapist. This would be a rational approach except that the assertions are, as shown, open to grave doubts.

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MALIGNANT BRENNER TUMOR

Report of a Case

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UNTIL recently Brenner tumors of the ovary have been considered as benign hormonally inactive tumors. This view has been accepted by numerous investigators since their classification by Robert Meyer in 1932.[1-5]

During the past few years, however, reports of cases have appeared in the European and American literature describing Brenner tumors which have undergone malignant degeneration. It is the purpose of this paper to present an additional case of Brenner tumor with subsequent malignant behavior.

Some of the first investigators to describe this tumor did regard it as a malignant neoplasm. Orthmann[6] in 1899 called his tumor "fibroma papillare superficiale carcinomatosum." Madellstamm[7] in 1932 quoted a case of Tavildaroff in which a second Brenner tumor was discovered in an ovary which was grossly normal two months previously at the time a Brenner tumor was removed from the opposite ovary. Madellstamm believed that the second tumor was a metastatic growth and stated that both tumors showed the typical morphology of Brenner tumors. This author classified all Brenner tumors as slow-growing carcinomas.

Bland and Goldstein,[8] in a review of 39 cases of Brenner tumor published in 1935, showed that, of 6 patients who died one year following operation, one patient probably died of metastases. It was not definitely indicated, however, that the metastases were of Brenner tumor origin.

Von Numers[9] described 2 cases of Brenner tumor in patients aged 50 and 56 years, respectively. In some areas of each the epithelial cells showed pleomorphism with hyperchromatic nuclei and numerous mitoses, as well as infiltrative growth. In one patient metastasis to the peritoneum was noted at the time of operation and both died within one year after operation.

Dubrauszky and von Massenbach[10] described a tumor, partly cystic and partly solid, which was removed from a woman 70 years of age who had been admitted for vaginal bleeding of two years' duration. The tumor showed typical Brenner epithelial nests in some areas. In other portions the authors described a continuous change between benign and malignant cell formation. The patient also had endometrial hyperplasia as an incidental finding.

Dubrauszky[11] later reported another case of malignant Brenner tumor, in many respects similar to the one he previously described. The second patient had had the left breast removed for carcinoma seven years before.

Rawson and Helman[12] in 1955 reported a case of malignant Brenner tumor which infiltrated both parametria with lymphatic spread to the left kidney. Some of the Brenner cell nests showed obviously malignant cells with invasive

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—The original tumor, showing an area of fairly typical Brenner morphology. (Low power.)
Fig. 2.—Sections taken from pelvic mass found at autopsy. (Low power.)
Fig. 3.—Islands of epithelial cells appearing within lymphatics and surrounding stroma. (Low power.)

behavior. An interesting conclusion was that radiotherapy given after the removal of the primary tumor had no effect on the inoperable portions of the tumor tissue.

More recently Mackinlay[13] described in a series of 9 cases of Brenner tumor, one with typical malignant characteristics. This author also mentioned a malignant Brenner tumor diagnosed by Dockerty.[14] Another case is that of Limburg[15] which was mentioned and illustrated by Novak.

A 68-year-old white woman was admitted to the Allentown Hospital on Jan. 31, 1955, complaining of lower abdominal pain and swelling of approximately four months' duration. She also complained of general weakness and anorexia and had lost 15 pounds since the onset of symptoms.

The abdomen was noted to be slightly distended, with moderate tenderness and a palpable mass in the left lower quadrant. This was described as ovoid in contour, freely movable, slightly tender, and approximately 20 cm. in diameter. Upon bimanual examination the previously described mass could be palpated and in addition the examiner noted that the mass had a cystic consistency.

At operation a large partly cystic tumor involving the left ovary was removed with the left oviduct, the uterus, and right adnexa. A cholecystectomy was performed one week later because of severe right upper quadrant distress, associated with cholelithiasis. Her recovery was satisfactory.

On Jan. 1, 1956, eleven months later, the patient was readmitted to the Allentown Hospital, at which time a nodular, moderately tender mass approximately 8 cm. in diameter was palpated in the region of the rectovaginal septum. Proctoscopic examination showed an abrupt stricture narrowing of the lumen of the rectum to a maximum diameter of 1.5 cm. This was felt to be extrinsic.

At operation a large pelvic mass was encountered. Portions of the rectosigmoid colon as well as loops of the small intestine were encompassed by the mass. Several plaquelike and miliary whitish granulomatous lesions were noted on the serosal surface of the small bowel. The tumor was considered inoperable and, after a small specimen was removed for biopsy, the abdomen was closed. The patient was discharged from the hospital on Jan. 20, 1956, as somewhat improved.

Shortly after discharge from the hospital she developed progressive abdominal distention and was readmitted on Feb. 4, 1956, with a diagnosis of obstructive ileus. Her condition deteriorated rapidly and she died on Feb. 6, 1956.

Pathological Examination.—Gross: The specimen obtained at the first operation consisted of the uterus, both tubes, and ovaries. The left ovary was completely replaced by a large ovoid cystic mass measuring 22 cm. in maximum diameter by 17 cm. in maximum thickness, with a weight of 3 kilograms. The outer surface was smooth and glistening, with roughening noted only at the site of detachment. The cystic portion of the tumor had a bluish color as viewed from the external aspect, with the solid portion being of yellowish-white color. On sectioning, approximately three fourths of the mass consisted of a large uniloculated cyst. This was lined by a creamy white velvety epithelium of soft spongy consistency which averaged 0.5 cm. in thickness. Within the lumen of the cyst there was 500 c.c. of clear straw-colored fluid. The solid portion of the tumor was yellow-white in color, with a firm somewhat rubbery consistency. Numerous minute cysts could be identified grossly. With the exception of several small intramural leiomyomas within the myometrium of the uterus, the remainder of the laparotomy specimen was not remarkable.

Microscopic: The solid portions of the tumor showed typical cell nests of transitional-type epithelium characteristic of the Brenner tumor (Fig. 1). These cell nests were ovoid or round in contour, many of them containing one or more cystic cavities lined by low columnar epithelium. Some of the epithelial cells were moderately pleomorphic and active proliferation was evident. A dense fibrous stroma composed of slender spindle cells

arranged in sheets and irregular fascicles surrounded the epithelial nests. The lining of the large cyst was composed of delicate fibrous stalks covered by multiple layers of uniform transitional cells.

The biopsy specimen submitted from the second operation on Jan. 10, 1956, consisted of a piece of yellow-white rubbery tissue of irregular contour measuring 1 cm. in maximum thickness. This revealed characteristic cell nests, some of which were undergoing cystic changes. The stroma was composed of fibrous tissue with areas composed of mature fat cells interspersed throughout.

At autopsy there was found a dense mass which measured 12 cm. in maximum diameter and which virtually filled the pelvis. The rectosigmoid colon was firmly embedded in the midportion of the tumor and the lumen of the colon was reduced to less than 1.0 cm. in diameter. The narrowing of the lumen was located 17 cm. from the anorectal junction. The proximal colon and distal two thirds of the small intestine were markedly distended. The mass itself was of dense rubbery consistency and of a yellow-white color. Tumor tissue replaced portions of the musculature of the colon and appeared as plaquelike nodules on the serosal surface of the ileum and jejunum. There was also approximately 3 L. of clear nonviscid yellow fluid within the abdominal cavity.

Microscopically the main mass was composed of dense fibrous stroma with islands of epithelial cells of transitional type (Fig. 2). These epithelial cell nests were rounded or ovoid although occasionally irregular in contour. The cells were for the most part well differentiated and of uniform appearance. An occasional cell nest showed some pleomorphism. In places cell nests were noted within the lymphatics (Fig. 3). Examination of numerous sections showed considerable variation of the stroma with some areas composed mostly of mature fat cells with very little fibrous tissue. Characteristic epithelial cell nests were encountered in these areas also. Cystic changes within the cell nests were noted but much less frequently than in the primary tumor. The metastatic nodules revealed typical transitional cell clusters with a more uniformly dense fibrous stroma composed of compact spindle cells.

Comment

Several interesting features of this case are deserving of emphasis.

The primary tumor measured 22 cm. in its maximum diameter and weighed 3 kilograms. This is not the largest of this type that has been reported in the literature but is rather striking considering the fact that most of the tumors are less than 5 cm. in diameter.

The solid portions of the tumor showed a pronounced tendency toward cystic degeneration with spaces lined by a single layer of medium height columnar cells of mucoid type. However, the large cyst was lined by a papillary type of epithelium composed of delicate fibrous stalks covered by many layers of transitional cells with no demonstrable epithelium of secretory type noted in any of the numerous sections.

With the exception of lymphatic invasion none of the sections of the primary tumor showed obvious malignant characteristics although atypical cells were sometimes noted. At autopsy the malignant nature of the tumor was obvious from the large pelvic mass and the numerous serosal nodules implanted on the small intestines.

Most of the microscopic sections from the mass and from the metastases revealed well-differentiated Brenner cell nests and stroma. The characteristic stroma was more consistently developed in the serosal implants, with a mixture of dense fibrous stroma and fat cells in the main mass. Atypicality of the

transitional cell nests was more frequently seen than in the sections from the original tumor and occasional lymphatics containing nests of these cells were noted. However, the marked pleomorphic changes common in most carcinomas were not seen.

Summary

The present report of a case of malignant Brenner tumor brings the total number described in the literature to eight, and adds further support to the recent observation that the Brenner tumor is not always a strictly benign lesion.

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OVARIAN ADRENAL REST TUMOR (MASCULINOVOBLASTOMA) SIMULATING ADRENAL VIRILISM

Report of a Case With Hormone Studies

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THE sudden appearance of a virilizing syndrome in a previously normal menstruating fertile woman presents an interesting diagnostic problem. The accurate delineation of the organ system responsible for the endocrine disturbance is paramount in selecting the most direct therapeutic approach to this problem. Adrenal and ovarian pathologic conditions are the two most usual sources of this type of virilization, and the differential diagnosis between these organ sites must be made. A case of virilization of ovarian origin recently studied, with detailed endocrinologic evaluation and eventual demonstration of a masculinovoblastoma of the adrenal rest tumor type, provides a typical example. The presurgical evaluation performed can illustrate and clarify the proper diagnostic approach to such problems. The excellent response to treatment, associated with resumption of menstrual regularity and fertility, indicates the degree of gratification that can be achieved by the removal of the inciting tumor.

The many names assigned to ovarian masculinizing tumors in the past have been based primarily upon the derivation of the tumor tissue. In some cases the assigned name is merely a descriptive term based upon the pathologic appearance of the tumor or the chief clinical features it presents. Thus, both Teilum[16] and Novak[11] have designated such tumors as "adrenal tumors of the ovary" or "ovarian hypernephromas," in the belief that the basic cell unit arises from aberrant adrenal cortical tissue. On the other hand, Glynn[4] favors the lutein cell as the parent cellular component of the neoplasms and he refers to them as "luteomas." In contrast, Rottino and McGrath[13] have coined a most descriptive but neutral term, "masculinovoblastoma," based on the most prominent clinical findings induced by the secretions of such tumors.

As implied by the variable nomenclature, there is no unanimity of opinion with respect to the cellular derivation of these tumors. The assumed origin has been based upon the clinically evident hormonal activity of the tumor itself, but few of the reported cases include hormone assays. Many of the tumors mimic the structural relationship noted in the cytoarchitecture of normal adrenal cortex. The columnar arrangement of the lipid-filled cells seen

in these tumors of ovarian origin may be indistinguishable from that of the adrenal cortex. The tendency of these tumors to secrete androgenic substances, associated with an increased 17-ketosteroid excretion, serves to differentiate them from other ovarian arrhenomimetic neoplasms, such as the arrhenoblastoma or luteoma. In the latter types, masculinizing effects are observed usually without concomitant elevation of 17-ketosteroid excretion levels.

The following case report illustrates the clinical and laboratory findings noted in an ovarian tumor of the adrenal rest type.

E. C., a 35-year-old Puerto Rican woman, was admitted for the first time on Oct. 7, 1955, because of amenorrhea of one year's duration, associated with increasing hirsutism and facial acne.

The patient had her menarche at the age of 12 and had regular periods every 30 days, lasting for 4 days. She had had three pregnancies terminating in full-term delivery of normal children, the youngest child being 6 years old. The patient had always been in good health and had never had an operation. For approximately 1½ years prior to admission, commencing early in 1953, she noted a change in her menstrual pattern. Her periods first became more frequent with menses being prolonged and lasting at times up to 14 days. In May, 1954, her periods ceased abruptly and she had had no vaginal bleeding or discharge since that date. A 20 pound weight loss over a 4 year period and an increase in facial acne in the year prior to admission were noted. She had always been moderately hirsute, but had never needed to shave her face. However, in the year before hospital admission hirsutism had increased greatly to the point of requiring shaving at least every other day. The patient was not aware of headaches, visual disturbances, polyuria, polydypsia, change in libido, or deepening of the voice. There was no significant decrease in the size of the breasts. The review of systems and family history were negative.

The pertient positive physical findings included facial acne and the recently shaved stubble of a dark beard on cheeks, chin, and upper lip. The breasts were normal. The blood pressure was 120/94, pulse rate 84 per minute, and respirations 18 per minute. The abdomen was moderately obese and hirsute with a male escutcheon. There were no abdominal masses or tenderness palpable. On pelvic examination the clitoris was hypertrophied. The remainder of the external genitals were normal. The cervix was in the axis of the vagina, and was slightly hypertrophied, with a small erosion at the external os which was closed. The corpus of the uterus was 1 degree retroflexed, normal in size, and smooth. The right adnexa were not palpated; the left ovary was thought to be enlarged by some observers, but not by others. The ovary was firm, mobile, and nontender.

Laboratory data obtained prior to admission showed the following: Five 17-ketosteroid determinations were elevated and ranged from 29.9 to 50.1 mg. per 24 hours. The pregnanediol determination was 0.52 mg. per 24 hours. Preoperative and postoperative hormone excretion levels are recorded in Table I and Fig. 1. The patient failed to demonstrate suppression of ketosteroid excretion on the oral administration of prednisone in doses of 10 mg. per day. Since a neoplasm was suspected in the light of this failure of response, the patient was admitted to the hospital for further diagnostic procedures.

On admission to the hospital, the urine report was negative. The hemogram showed 4.52 million erythrocytes per cubic millimeter, a hemoglobin determination of 14 Gm. per cent, and a normal leukocyte count and differential. The erythrocyte sedimentation rate (Westergren) was 6 mm. in 1 hour. The total eosinophil count was 333 per cubic millimeter. The fasting blood sugar was 99 mg. per cent and the nonprotein nitrogen was 23 mg. per cent. An intravenous hydrocortisone test was performed with 100 mg. of hydrocortisone in 1,000 ml. of 5 per cent glucose infused over an 8 hour period. Urine

specimens were obtained for 8 hours before, during, and after the infusion, and 17-ketosteroids were determined. No change in the level of 17-ketosteroid excretion was noted. As a result of these findings, it was felt that the virilizing process was due to a neoplasm, an autonomously secreting unit. X-rays of the chest and an intravenous pyelogram were normal.

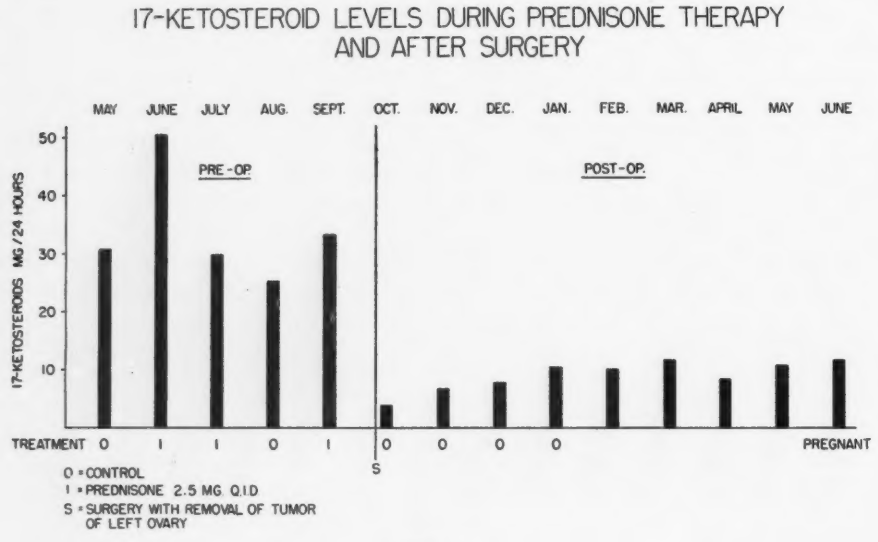
17-KETOSTEROID LEVELS DURING PREDNISONE THERAPY AND AFTER SURGERY
MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC. JAN. FEB. MAR. APRIL MAY JUNE
17-KETOSTEROIDS MG./24 HOURS
50
40
30
20
10
PRE-OP.
POST-OP.
TREATMENT 0 1 1 0 1 S 0 0 0 0 PREGNANT
0 = CONTROL
1 = PREDNISONE 2.5 MG. Q.I.D
S = SURGERY WITH REMOVAL OF TUMOR OF LEFT OVARY

Fig. 1.

TABLE I. RESPONSE OF 17-KETOSTEROID AND PREGNANEDIOL LEVELS TO ORAL AND INTRAVENOUS CORTICOID THERAPY AND SURGERY

DATE	TREATMENT	17-KETOSTEROID (MG./24 HOURS)	PREGNANEDIOL (MG./24 HOURS)
Preoperative.—			
5/ 9/55	Control	31.2	—
6/13/55	Prednisone, 2.5 mg. q.i.d. for 4 weeks	50.1	—
7/18/55	Prednisone, 2.5 mg. q.i.d. for 5 weeks	29.1	—
8/15/55	Control	25.1	0.52
9/19/55	Prednisone, 2.5 mg. q.i.d. for 5 weeks	33.9	
10/11/55	Control 0 to 8 hours	5.9	0.15
	Hydrocortisone, 100 mg. infusion 8 to 16 hours	15.1 *	—
	Control 16 to 24 hours	10.3	—
10/12/55	Control 24 to 30 hours	10.8	0.19
Operation.—			
10/14/55	—	—	—
Postoperative.—			
10/19/55	—	4.4	—
10/20/55	—	6.7	—
11/21/55	—	7.7	—
12/12/55	—	10.6	—
1/16/56	—	10.1	—
3/15/56	—	12.0	—
4/ 2/56	—	8.4	—
5/ 7/56	—	11.1	Pregnant
6/11/56	—	12.3	Pregnant

*mg./8 hours.

Since the left ovary was thought to be enlarged by some on physical examination, exploratory laparotomy was done with a view to checking both adrenal glands if significant ovarian pathology were not uncovered. A left oophorectomy was performed on Oct. 14, 1955, through a lower paramedian incision. The ovary was 8 to 10 cm. in diameter, pearly white in appearance, and contained numerous small cysts. On section, it contained a well-circumscribed 5 cm. solid orange tumor (Fig. 2). The right ovary was kidney shaped and about twice normal size. The capsule and cortex were thickened, but on section no further abnormalities were noted. A wedge resection of the right ovary was performed. The histology of the tumor of the left ovary can be seen in Figs. 3*A* and 3*B*.

Fig. 2.—Cross-section showing well-circumscribed tumor mass surrounded by compressed ovarian tissue.

The postoperative course was uneventful. The patient had a normal 5 day menstrual period on Nov. 9, 1955, 25 days following removal of the ovarian mass. Postoperative ketosteroid excretion levels can be seen in Table I and Fig. 1. Menses were once again regular until her last menstrual period on April 20, 1956, when amenorrhea again occurred. Pelvic examination on June 18 revealed enlargement of the uterus, and a pregnancy test subsequently performed was positive. The patient delivered a full-term normal female infant on Jan. 28, 1957.

Comment

The similarity between this case and that reported by Rottino and McGrath[13] is striking, with reference to both the gross and microscopic appearance of the tumor and the clinical picture, even to the point of ensuing pregnancy. The differential diagnosis in this patient, when first seen, included the possibility of adrenocortical hyperplasia of the postpubertal type. However, with the failure of oral corticoid therapy to depress the elevated 17-ketosteroids to normal levels, an intravenous test with hydrocortisone was done. Inasmuch as there was still no significant depression of the level of ketosteroids with the corticoid infusion, it was assumed that a neoplasm of the adrenal or ovary was producing the virilism. A review follows of the physiologic concepts on which this assumption was based.

Normally, the fasciculata zone layer of the adrenal cortex, under ACTH stimulation, metabolizes cholesterol to hydrocortisone: cholesterol is converted to pregnanolone, then to progesterone, 17-OH progesterone, and, ultimately, by an enzymatic process, to hydrocortisone.[5, 6] The enzymatic process

Fig. 3*A*.—Low-power microscopic view showing fibrous capsule separating neoplastic tissue on the left and normal ovarian tissue on the right.

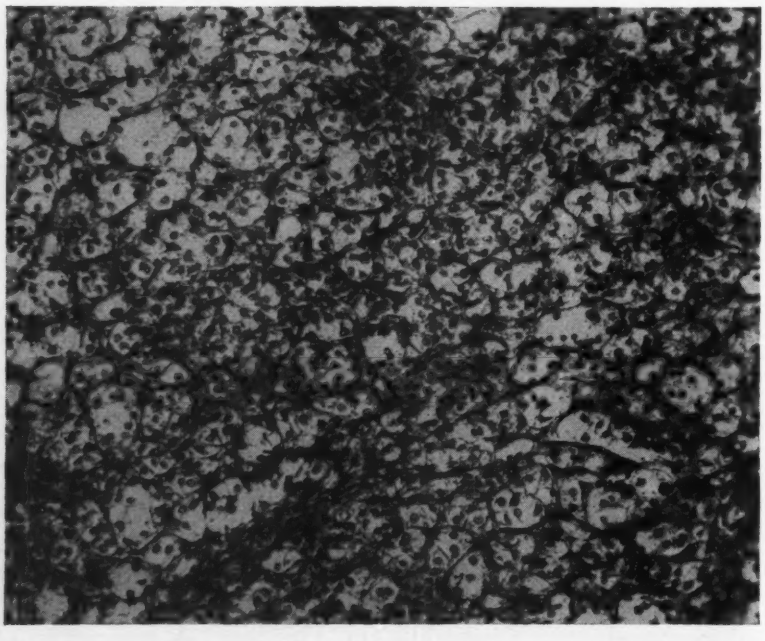

Fig. 3*B*.—High-power view of neoplastic tissue showing adrenal cytoarchitecture in cordlike arrangement.

which converts 17-OH progesterone to hydrocortisone facilitates hydroxylation at C-21 and C-11. In patients with the adrenogenital syndrome, there is a defect in this metabolic pathway whereby 17-OH progesterone is not converted to hydrocortisone in the usual manner.[2] Thus, the inhibitory effect of hydrocortisone upon ACTH secretion is not operating, and increased amounts of ACTH are released from the pituitary.[15] This may result in one of two phenomena. First, an increased production of 17-OH progesterone which is degraded into androgenic steroids occurs. The latter steroids are responsible for the manifest virilization.[8] These steroids will also decrease pituitary gonadotrophin production and release so that defeminization with cessation of ovarian function ensues. In addition, the increased ACTH secretion resulting from the inefficient hydroxycorticoid production may stimulate the direct production of androgenic substances (17-ketosteroid precursors) via the zona reticularis.[2, 10, 14] The end effect of masculinization, and defeminization secondary to suppression of pituitary gonadotrophin secretion, results from either mechanism. Administration of exogenous corticoids should suppress the excessive ACTH secretion and thereby decrease the abnormal production of androgens with associated decrease in 17-ketosteroid excretion.[15] Failure of this to occur following either oral or intravenous corticoid therapy implies that an autonomous neoplastic process of the adrenal cortex or ovary must be considered as the source of virilization.[10, 14]

The suspicion of an enlarged ovary simplified the choice of surgical approach, inasmuch as pelvic exploration was indicated prior to examination of the adrenal cortex. The presence of the orange tumor in the ovary confirmed the impression of the neoplastic nature of the patient's disease and made exploration of the adrenal glands unnecessary. The prompt decrease in 17-ketosteroids after removal of the tumor (Table I and Fig. 1) and the resumption of normal ovarian function, followed subsequently by pregnancy and delivery of a normal full-term infant, confirmed the endocrine nature of the tumor. Significant levels of 17-ketosteroids were extracted from the tumor.

HORMONE LEVELS OF TUMOR TISSUE

Estrogenic activity	4.1 rat units/Gm.
Ketosteroids (Zimmermann reaction)	5.7 mg./Gm.
Formaldehydogenic substances	0.29 mg./Gm.
Silber-Porter chromogens	1.46 mg./Gm.
Pregnanediol	0*
Pregnanetriol	0

*No absorption peak between 390 and 460 μ.

Tumors such as those described in the cited case are not common. The first was described in 1908 by Bovin.[3] In 1921 Glynn reported another.[4] Subsequent extensive reviews of the literature were made by Kepler[9] and Iverson,[7] who accepted 14 and 15 cases, respectively. Palmer and Waldrop,[12] in 1957, added one more case. Whatever the actual number of authentic reported cases,[1, 12, 16] it must be admitted that the figure is small enough (in the range of 30) to justify reference to this particular tumor as rare.

Grossly, the tumors are usually well encapsulated, round or oval, 2 to 16 cm. in diameter, and yellowish orange in color. Most frequently the remaining ovarian tissue is compressed to one side, and the tumor itself may show septic changes. The tumor in this case fulfills these criteria. Microscopically, the tumor is composed of large polyhedral cells arranged in columns. These are placed within a delicate vascular fibrous stroma. The cells themselves are filled with lipid, and special fuchsin stains show fuchsinophil granules in the cytoplasm. Because of the close resemblance of the present tumor to adrenal cortical cytoarchitecture (Fig. 3*B*) associated with the demonstration of 17-ketosteroid production and content, the term "adrenal rest tumor" seems appropriate.

Summary

A case of spontaneous virilism caused by an adrenal rest tumor of the ovary in a previously normal menstruating woman is presented and the differential diagnostic approach to the problem of the adrenal genital syndrome considered. Remission of the clinical picture with a lowering of 17-ketosteroid excretion levels on corticoid therapy indicates hyperplasia rather than neoplasia, and the appropriate therapy is medical. Persistent elevation of 17-ketosteroids despite corticoid therapy, as observed in this patient, points to a tumor of either the adrenal cortex or ovary. Here treatment is surgical removal of the tumor. If any doubt is present as to the exact location of the neoplasm, an abdominal approach with examination of the pelvic organs first appears wisest and simplest. Pelvic examination, intravenous pyelogram, and presacral perirenal air insufflation may be helpful in localizing the neoplasm.

Appreciation is expressed to Dr. C. O'Donovan of The Upjohn Company for the intravenous hydrocortisone used in this study. We are also grateful to Dr. J. Black of the Schering Corporation for the supplies of prednisone (Meticorten) used in this study.

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METASTATIC BREAST CARCINOMA IN THE OVARY*

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METASTATIC carcinoma of the ovary has been a focus of interest since Krukenberg described this lesion in 1896. This clinical entity is of interest both from the problem of clinical diagnosis and of the mechanism by which the metastatic carcinoma gains access to the ovary.

Recently we have performed a series of oophorectomies on patients with carcinoma of the breast. We were surprised to find a high incidence of metastatic breast adenocarcinoma in these ovaries. Some of these metastatic masses in the ovaries were large enough to be palpable vaginally, and on occasions such masses have presented problems in diagnosis.

This study is to call attention to the frequency of this clinical entity and to review the pathologic anatomy for evidence of the metastatic mechanism. The literature during the last 25 years reveals many reports of breast carcinoma metastatic to the ovaries and the figures on incidence vary. Many are single case reports. There are, however, a few large series reported. For example, Crile[1] reported 520 cases of breast carcinoma and noted clinically only one case of ovarian metastasis. Willis[2] reviewed metastatic growths in 45 necropsied cases of primary breast carcinoma and found ovarian involvement in 3 cases. James Ewing[3] cited Gross to have found ovarian metastases in 8 per cent of 423 necropsied cases of breast carcinoma. Warren and Witham[4] reported unilateral or bilateral involvement in 15 of 162 such cases. Others, however, have reported a higher number in autopsy material, ranging as high as 10 per cent. Probably the more advanced the phase of disease studied, the more likely that ovarian metastases will be seen. The impression expressed by several investigators was that the incidence is probably higher than the literature indicates and that a more thorough search would raise the occurrence figure. A higher incidence noted in more recent reports probably parallels an increased interest in the palliative treatment of recurrent breast carcinoma, for in these cases continued study and careful observation of the patients establishes a more accurate rate and location of metastases.

Our material is taken from a group with treated carcinoma of the breast with evidence of recurrent disease, receiving palliative therapy. Clinically we are more interested in the incidence of ovarian metastases in this stage of the breast carcinoma than in the autopsy material. These are the patients who

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may have a palpable ovarian tumor presenting a diagnostic problem. We studied 91 patients who had oophorectomy in our institution, 23 of whom, or 25 per cent, had metastatic disease to the ovaries; 16 cases, or 70 per cent, were bilateral. In 3 patients of the 23 with ovarian involvement only unilateral oophorectomy was performed because of previous surgical extirpation of the other ovary; in only 4 cases where both ovaries were studied was unilateral disease present.

Another point of clinical interest was whether the disease ever produced autocastration. One would suspect that this would be very unlikely because of the marked reserve of the ovary and the fact that very little ovarian tissue need be preserved to function adequately. We know that ovaries involved with primary neoplasms continue to function even though largely replaced by tumor. We wondered if the embolic process, the ovarian vascular alteration, or the metastatic mechanism might be different in this situation from that occurring with a primary ovarian neoplasm and thereby alter ovarian physiology.

Microscopic review of the ovaries from patients still menstruating showed active ovulation with formation of corpora lutea. Thirteen of the 23 patients, or 56 per cent, were still menstruating; the remaining 10 had a spontaneous menopause at the expected age, and one had an x-ray induced menopause. No symptomatic evidence of ovarian dysfunction was elicited in the group below menopausal age. Apparently, then, the metastatic disease within the ovary produced no discernible alteration in this physiology, and autocastration rarely occurs.

The mechanism by which the metastatic carcinoma obtains entry to the ovary has been subject to some speculation and investigation. The three routes suggested are: Direct surface implant from peritoneal seeding; this may be facilitated in the ovulating ovary by the defect in the surface of the ovary when ovulation occurs. We have searched these ovaries for microscopic evidence of this process. Lymphatic spread by way of the hilum, and arterial or venous spread to the ovary are other possible routes.

According to Barzilai,[5] carcinoma of the breast may metastasize to the ovary by extension of tumor cells through the lymphatics of the deep fascia pectoralis, downward through the abdominal wall to the epigastric region, and then through the lumbar nodes by the same route as carcinoma originating in the upper gastrointestinal tract; also through the blood stream, and by direct extension to the pleura and the diaphragm, then to the peritoneum, and thence, by continuity or by implantation of free tumor cells, to the ovarian surface.

Jaki and Korpassy[6] noted that hematologic spread and implantation are facilitated by the spiral course of the ovarian arteries. The blood pressure drops toward the surface of the ovary because of the spiral shape and this facilitates spread of the cancer cells.

Reviewing the vascular anatomy of the ovary, Reynolds and associates[7, 8] stated that in the normal adult ovary, "The main ovarian artery as it courses in the hilus of the ovary is noted to be undulant, tortuous, with a degree of flattening. . . . The branches . . . proceed from the hilus into the ovary in a parallel manner reminiscent of the teeth of a rake. . . .

"Primary, secondary, and tertiary degree branches are noted arising from the main artery in the hilus. The primary trunks are usually tortuous or undulant with an occasional spiral. They are also usually flattened. The degree of crowding together among the various branches is dependent upon the presence and size of specialized structures in the ovary . . . the veins of the ovary drain into a pampiniform plexus in the hilar area. They are large, irregularly tortuous, markedly flattened, and often appear matted. . . . The various branches anastomose with each other very frequently. This contrasts with the ovarian arteries which show no evidence of vascular anastomoses. Within the substance of the ovary, the veins end in small, straight channels that are never spiralled.

"In the course of injecting blood vessels in a series of about 60 pairs of human ovaries, observations were made on the distribution and character of the secondary and tertiary blood vessels in the human ovary. It was clear that in the absence of estrogen these vessels undergo progressive involution and eventually disappear. They are highly developed, dense, and numerous only in the presence of estrogen. This fact might have some bearing on the microscopic appearance and distribution of the metastatic carcinoma in the ovaries in pre- and postmenopausal age groups."[8]

Of the 23 cases there was predominance in the younger age group.

30 to 39 years	10
40 to 49 years	7
50 to 59 years	5
60 to 69 years	1

With the details of vascular anatomy in mind, we undertook to study the microscopic pathology of these ovaries to determine the mechanism of metastases. It was soon evident that tumor emboli were present in vessels of varying sizes. There was no stromal or round-cell reaction to the metastatic tumor. Metastatic nodules were closely associated with Graafian follicles and corpora lutea, and seemed not to affect this ovarian function in any way. There was no significant parasitic diversion of the blood vessels to the tumor or appreciable increase in vascularity.

There were 7 cases where surface implantation was suggested; in these cases other serosal implants were present in the abdomen, making surface implantation possible. Tumor was present in the corpus luteum in 2 of these. There were 11 cases in which hilar metastases were suggested. Five of these 11 showed tumor in the artery; 2 of these showed wedge-shaped distribution of the lesion, and 4 showed tumor emboli in the lymphatic vessels. Four cases showed diffuse seeding without any discernible pattern. One case showed a mixed pattern.

Summary

We have reviewed 91 cases of oophorectomy done for breast carcinoma and found 23 cases, or 25 per cent, with metastatic disease in the ovary. A clinical review of the patients' ovarian functions involved in metastatic breast

carcinoma showed no alteration. A review of the microscopic pathology indicated multiple mechanisms of metastases. The breast carcinoma may gain entrance to the ovary both from the surface and through the hilar vessels. Bilateral involvement was common and the ovarian masses resulting from the metastatic involvement were occasionally large enough to be palpable vaginally. In these cases it was impossible to eliminate primary ovarian disease.

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BENIGN CERVICAL EROSION IN NONPREGNANT WOMEN OF CHILDBEARING AGE*

A Colposcopic Study

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BENIGN cervical erosion is one of the most frequent findings noted in pelvic examination.[1, 2] It has been evaluated by cytologic studies, very exhaustively by histopathologic investigations, but quite rarely by colposcopy.[3-5] Since colposcopy (magnified stereoscopic visualization of the cervix under bright illumination) affords a panoramic view of the cervical portio and refines gross inspection, we believe it can add to our knowledge of benign as well as malignant cervical change. Hence the use of colposcopy in this study.

The term cervical erosion is a clinical one indicating an area of velvety reddening of varying intensity and extent surrounding the anatomical external cervical os. Many names are used more or less interchangeably, some with connotations of mechanism or causation: cervicitis, endocervicitis, eversion, ectropion, pseudoerosion, diseased cervix, and, much less commonly, misplaced or heteroplastic endocervical tissue,[6] vermilion halo,[7] and mucoepithelial hyperplasia.[8] Various self-explanatory adjectives are also applied: simple, follicular, glandular, papillary, cystic, friable, polypoid, nonspecific, ulcerative, chronic, congenital, and acquired. The prime symptom of erosion is leukorrhea; occasionally there is bleeding. Grossly, the cervix may suggest malignant change. The true nature of the lesion cannot be determined by naked-eye inspection and further evaluation may be necessary to ascertain more definitely the presence or absence of malignancy. Our aim in this study is to determine what is present colposcopically when a woman has a benign cervical erosion, including an attempt to ascertain whether there is a loss of surface epithelium, as some[9, 10] believe, or whether a covering surface epithelial layer is present.[11-13] To simplify matters we have chosen to limit our investigation to nonpregnant women of the childbearing age.

Method of Study

Our material is drawn from all cases seen since the start of our Colposcopic Clinic four years ago. Only cases of cervical erosion which showed no evidence of atypism or malignancy by both cytologic and histologic means are included in this series. A group of cervices thought to be intact and smooth was also studied.

As described by Hinselmann,[14] there are three major normal cervical findings by colposcopy. First, the cervical portio may be *intact,* covered solely

*Presented at a meeting of the Obstetrical Society of Philadelphia, Jan. 3, 1957.

Fig. 1.—Colpophotograph and diagram of a so-called benign erosion which is probably congenital in origin. The patient is a 20-year-old white nulligravida. Note that the "erosion" is essentially an area of columnar epithelium.

a, Fold of vaginal epithelium; *b*, ectopy (perioral columnar epithelium); *c*, rim of colposcopic leukoplakia; *d*, arbor vitae arrangement of columnar epithelium; *e*, external os; *f*, highlights.

by squamous epithelium. Second, there may be an area of *ectopy* ("ectopic" columnar epithelium) around the anatomical external os. This is sharply limited from the peripheral squamous epithelium. The third finding is a mixture and intermingling of squamous and columnar epithelium, the *transformation or regeneration zone;* this is characterized by (a) islands of columnar in squamous epithelium, (b) gland openings in squamous epithelium, and (c) Nabothian cysts. These major findings have all been demonstrated to be benign histologically and their presence is practically complete assurance of the benign condition of the portio.[15] It is of course possible by colposcopy to determine whether a given area of the portio is covered by squamous or columnar epithelium and whether the area is denuded of epithelium.

Our technique of colposcopic examination is simple.[16] Briefly, it consists of gently inserting the speculum, adjusting the colposcope, and then inspecting the cervix, first without manipulation, after gently swabbing with a cotton ball, after the application of 3 per cent aqueous acetic acid, and finally after the application of Lugol's solution (Schiller test). Acetic acid is especially important for the identification of columnar epithelium since for a minute or two following its use the epithelium assumes a characteristic white, bubbly appearance. Before acetic acid, columnar epithelium appears red and smooth since the underlying vascular stroma easily shines through. We personally use the Moeller colposcope and prefer 10× rather than 20× magnification.

We were able to find 137 nonpregnant women of childbearing age (16 to 44 years) who were referred to the Colposcopy Clinic because of a cervical erosion and in whom smears and subsequent biopsy were both completely benign. The usual diagnosis histologically was "chronic cervicitis." There were 44 nonpregnant women of the same age range, in whom the cervix, by well-qualified examiners, was classified as intact, i.e., covered solely by squamous epithelium according to naked-eye inspection with adequate light. All these latter cases had negative cytologic smears; about one third were also subjected to biopsy and all these were negative. It is a fair assumption that the others were normal histologically. Approximately three fourths of the women in both series had been delivered of at least one child vaginally.

Results

The colposcopic findings of the 137 benign erosions are listed in Table I.

TABLE I. LISTING OF COLPOSCOPIC FINDINGS OF 137 NONPREGNANT WOMEN OF CHILDBEARING AGE WITH CERVICAL EROSION, KNOWN TO BE BENIGN

Ectopy	129	94%
Gland openings in squamous epithelium	123	90%
Nabothian cysts	50	37%
Increased vascularization	26	19%
Islands of columnar epithelium	21	15%
Ground leukoplakia	8	6%
Simple leukoplakia	4	3%
Mosaic leukoplakia	3	2%
True erosions (ulcer)—traumatic	2	2%

The most frequent findings were ectopy and gland openings in squamous epithelium. In decreasing order were Nabothian cysts (most of them too tiny to be visible grossly), increased vascularization, and islands of columnar epithelium. Increased vascularization was always found to explain the reddening when there was no ectopy. All but one cervix demonstrated some colposcopic evidence of columnar epithelium on the portio. This particular cervix

Fig. 2.—Colpophotograph and diagram of a more common type of so-called benign erosion. The patient is a 26-year-old Negro woman, gravida ii, para ii. Note that the "erosion" is actually an irregular area of perioral columnar epithelium (ectopy) surrounded by a zone with mixture of columnar and squamous epithelium (transformation zone).

a, Gland openings; *b*, columnar epithelium (ectopy); *c*, island of columnar epithelium surrounded by increased vascularization; *d*, highlights; *e*, tongue of squamous epithelium growing toward the external os; *f*, old laceration at 6 o'clock; *g*, island of columnar epithelium; *h*, external cervical os.

showed a marked vascular pattern accounting for the reddened appearance surrounding the os. Much less frequent in occurrence were the three forms of colposcopic leukoplakia[4, 14, 16]: simple leukoplakia, ground leukoplakia (whitening with a stippled pattern), and mosaic leukoplakia (whitening in a mosaic pattern). In only 2 cases were true erosions seen; each of these was traumatic, occurring at the periphery of the cervix and noticeable only by the colposcope. They were presumably due to speculum insertion.

Other findings of interest were noted. The squamous epithelium often seemed to be growing toward the os by sending in tongues of epithelium into columnar epithelium. Squamous epithelium in the area of the transformation zone frequently took the iodine stain poorly, presumably indicating epithelial proliferative activity. Wherever columnar epithelium met squamous epithelium there was often a rim of colposcopic leukoplakia (whitening from opacity as a result of epithelial thickening). As for the columnar epithelium, there was a variation in its texture from cervix to cervix. At times an arbor vitae appearance was noted. Nabothian cysts were, as might be expected, usually found at the periphery of the transformation zone.

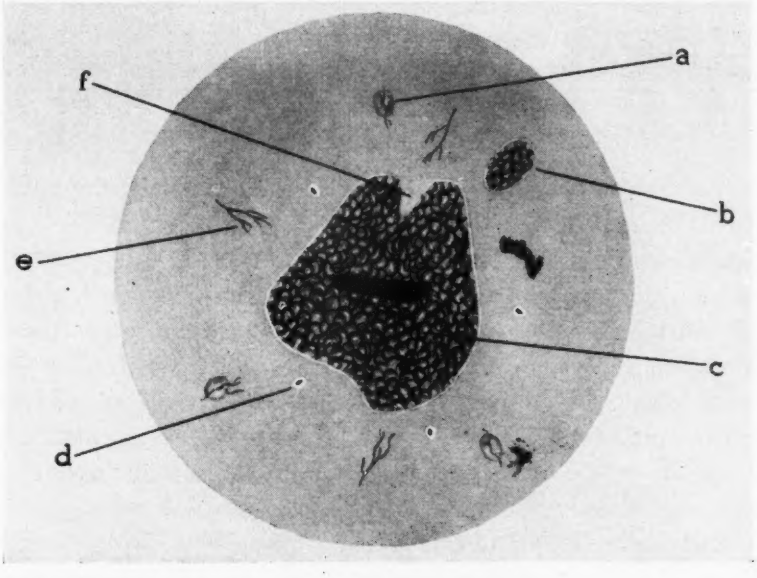

Fig. 3.—Composite sketch of a "typical" cervical erosion.
a, Nabothian cyst; *b*, island of columnar epithelium; *c*, ectopy (columnar epithelium around external os); *d*, gland opening; *e*, increased vascularization; *f*, tongue of squamous epithelium growing toward the os.

In only eight of the 137 cases did the erosion noted clinically prove to be solely an area of ectopy colposcopically, i.e., composed solely of columnar epithelium without surrounding transformation zone. The ages of these women ranged from 16 to 41 years (16, 16, 18, 20, 22, 23, 40, 41). Four of these had never been pregnant; the others had been delivered of at least one child vaginally. Statistically, in line with the findings of Ganse,[3] ectopy seemed to occur more in younger women than ectopy plus transformation zone, although a larger series of cases is necessary to be certain.

As a form of control, 44 cervices considered intact by other staff men were also evaluated by colposcopy. The findings are listed in Table II. In 20 cases, gland openings were present on the portio. Ectopy occurred in 8

cases, Nabothian cysts in 6, and islands of columnar epithelium in one. There were 4 instances of the three types of colposcopic leukoplakia, all on portios with a transformation zone. In other words, cervices which appeared grossly intact sometimes exhibited, but to a lesser degree, the changes of those that clinically demonstrated a benign erosion.

Colpophotographs and diagrams of 2 benign so-called cervical erosions are to be found in Figs. 1 and 2. The former illustrates ectopy; the latter ectopy and transformation zone, the usual combination of findings. Fig. 3 is a composite sketch of the more typical colposcopic findings in cases of cervical erosion, showing ectopy and a more peripheral transformation zone (islands of columnar epithelium, gland openings in squamous epithelium, and Nabothian cysts) and increased vascularization.

TABLE II. LISTING OF COLPOSCOPIC FINDINGS OF 44 NONPREGNANT WOMEN OF CHILDBEARING AGE WITH THE CERVIX THOUGHT TO BE INTACT BY NAKED-EYE INSPECTION

Gland openings	20	46%
Ectopy	8	18%
Nabothian cysts	6	14%
Islands of columnar epithelium	1	2%
Simple leukoplakia	2	5%
Mosaic leukoplakia	1	2%
Ground leukoplakia	1	2%

Comment

It is important to attempt correlation of the above-mentioned colposcopic findings with the accepted histologic picture of cervical erosion. The lack of true erosion (ulceration) has been noted colposcopically by others[3, 15] in larger series of cases. Histologically, superficial ulceration may be found on biopsy. However, it must be realized that this does not necessarily represent the true state of affairs in vivo since the curettage which may precede the biopsy or the trauma of taking the biopsy itself, with subsequent handling, may lead to loss of surface epithelium. Moreover, it is unlikely that a chronic superficial benign ulceration would exist permanently. Inflammation manifested colposcopically by increased vascularization is often paralleled by evidences of inflammation histologically. The transformation zone is explicable by the frequent findings of both types of epithelium together with epidermidalization in tissue sections. It seems from examination of the two groups of cervices that columnar epithelium occurs more often than is suspected on the cervical portio and that the presence of columnar epithelium in an isolated biopsy specimen is no proof that the tissue is from the endocervix. It is conceivable also that adenocarcinoma could arise from the columnar epithelium of the portio.

The presence of tongues of squamous epithelium, the islands of columnar in squamous epithelium, the gland openings, and the Nabothian cysts which tend to be at the periphery of the transformation zone, together with the lack of squamous islands in columnar epithelium, all seem to indicate progressive growth of the squamous epithelium toward the os. This concept is given some support by the observation that the atrophic cervix of later life rarely shows columnar epithelium on the portio. There seems to be an indication, too, that

the average cervix in the childbearing age has many squamocolumnar junctions rather than one as is so often assumed. The presence of the three forms of leukoplakia as seen by the colposcope is to be expected in a transformation zone[14] and indicates that abnormal epithelial growth forms occur in such an area. The frequent non-iodine staining character of the squamous epithelium in this site probably results from increased glycolysis from growth and regeneration.

Conclusions

1. Studied colposcopically, benign cervical erosion of nonpregnant women of the childbearing age usually consists of a rim of ectopy about the os (columnar epithelium) surrounded by a transformation zone consisting of: (a) columnar epithelium in the form of isolated islands, (b) gland openings in squamous epithelium, or (c) Nabothian cysts. There may be increased vascularization.

2. True erosion (loss of surface epithelium) is apparently very rare.

3. Benign cervical erosion appears red because of vascular stroma showing through thin columnar epithelium, or because of increased vascularity.

4. Benign cervical erosion as seen clinically represents a more advanced stage of a condition observable with the colposcope even in cases which the naked eye may interpret as "intact," i.e., a portio covered solely by squamous epithelium.

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REGRESSION, RECURRENCE, AND REGRESSION OF EPITHELIAL ATYPISM OF THE CERVIX AS INDICATED BY CYTOLOGIC SMEAR, COLPOSCOPIC FINDINGS, AND SCHILLER IODINE STAINING*

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ATYPICAL cervical epithelium may apparently be produced by inflammation, by reparative-regenerative processes, or by hyperhormonal states such as pregnancy. It may occur without any specific known cause. Such epithelium may later return to normal, and become atypical again later. It is just such a case that we would like to report.

Case Report

M. R., a 27-year-old Negro woman, separated from her husband, gravida iv, para iii, was first seen at the Medical Clinic of the Jefferson Medical College Hospital in March, 1951. Pelvic inflammatory disease was diagnosed and the patient was referred to the Gynecology Clinic. The patient, however, did not return until six months later when she registered at the Obstetric Clinic. Prenatal studies were normal; blood Wassermann and Kahn tests were negative. The cervix elicited no special comment from various examiners. No cytologic smear was taken at this time. After an uneventful prepartum course, the patient was delivered of normal, premature binovular twins in February, 1952.

At ten weeks post partum, because the cervix seemed unduly red, cytologic smears were taken and classified as doubtful because of atypical cells (Papanicolaou Class II). Two spot biopsies were taken. These showed "chronic cervicitis." No curettage was done at this time.

Although instructed to continue to have follow-up examinations, the patient did not do so. Not until several years later, in January, 1955, did she report to the Accident Ward because of rectal pain. She was immediately admitted to the Gynecology Ward with a diagnosis of severe pelvic inflammation. The patient stated she had had another delivery at another institution several years ago subsequent to the last one mentioned. While in the hospital with the pelvic inflammation, and in spite of penicillin, the patient had a spiking temperature to 102° F. for a week. Pelvic findings disclosed bilateral tenderness, bilateral induration, and an ill-defined mass behind a normal-sized retroverted uterus. In several days the mass became fluctuant and spontaneously ruptured into the rectum; after this the patient experienced relief of symptoms and her temperature gradually returned to normal.

At the time of this particular admission, interest centered on the cervical portio. Clinically, the cervix showed minimal perioral reddening, i.e., an "erosion." Several cervical cytologic smears were reported as "doubtful" (Papanicolaou Class III) and "suspicious"

*Presented at a meeting of the Obstetrical Society of Philadelphia, April 5, 1956.

(Papanicolaou Class IV). There was marked dyskaryosis and fiberlike cells were seen. Colposcopic examination showed mosaic leukoplakia (whitening in a mosaic pattern)[1, 2] (Fig. 1, *A*). The cervix did not stain with aqueous iodine by the Schiller test.[3] Since the result of each one of these three special methods of evaluation of the cervix was unusual, cervical biopsy was indicated; it was not done, however, because of the severe pelvic inflammation.

Subsequent to her discharge from the hospital and at follow-up in the Gynecology Outpatient Department the pelvic induration gradually lessened. Cytologic, colposcopic, and iodine-staining findings remained the same in June, 1955, as in January, 1955.

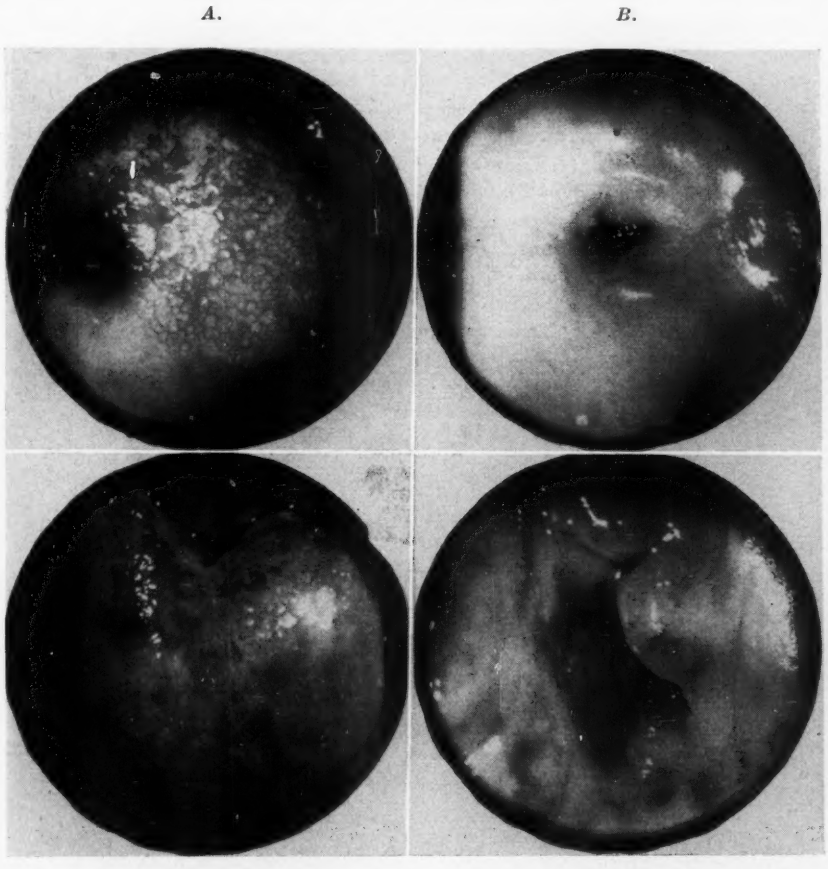

Fig. 1.—Serial colpophotographs. *A*, Shows mosaic leukoplakia as seen initially at the time of severe inflammatory disease. The cervical os is at 1 o'clock; the dark area at 9 o'clock is an artifact. *B*, Illustrates the complete regression of the above, 9 months later without any local therapy. Biopsy at this time showed "chronic cervicitis." *C*, Shows the cervix 6 months after biopsy; mosaic leukoplakia is again apparent. (The histologic findings at this time are depicted in Fig. 2.) *D*, Illustrates the cervix 6 months later just before radical hysterectomy. The cervical portio is irregularly healed and there is some exposed columnar epithelium. At 3 o'clock there are punctate areas of telangiectasia.

After several letters the patient returned to the Colposcopic Clinic in September, 1955. At this time pelvic findings were quite normal without tenderness or fixation. By speculum inspection the cervix seemed only slightly reddened. Surprisingly, cytologic smears were completely normal (Papanicolaou Class I). Colposcopic examination now showed a completely intact-appearing portio covered with apparently normal squamous epithelium which took the iodine stain (Fig. 1, *B*). The patient had taken no medication

nor had the cervix been treated since the episode of pelvic inflammation mentioned previously. Curettage and biopsy were recommended but the patient refused admission. In lieu of this, four large spot biopsies (including the whole portio surrounding the external os) were taken. Careful study and later review of these biopsies showed only "chronic cervicitis."

After visiting another hospital several weeks previously where she had been treated for a recurrent, but mild, pelvic infection, the patient returned to our institution in early March, 1956. Cytologic findings were again reported as "suspicious" for malignancy (Papanicolaou Class IV). Neither at this nor at other examinations were Trichomonads found by wet smear. Once again an extensive mosaic leukoplakia was present colposcopically and the cervix again failed to take the iodine stain (Fig. 1, *C*). The sedimentation rate and white-cell count were normal and there was no clinical evidence of pelvic inflammatory disease. The patient was hospitalized and a fractional curettage (productive of no endocervical curettings) and an extensive circular cervical biopsy excising all the non-iodine-staining portio were performed. The endometrium showed "late secretory endometrium." There was some disagreement with respect to the cervix among various members of the Department of Pathology. The slides were then sent to three outside pathologists with diagnoses ranging from severe atypism to extensive carcinoma in situ. The final diagnosis by Dr. P. A. Herbut, Professor of Pathology at Jefferson Medical College, however, was "squamous cell carcinoma with early invasion" (Fig. 2).

Fig. 2.—Biopsy of the cervix taken at the second occurrence of mosaic leukokplakia. Opinions varied but the "official" diagnosis was early invasive squamous-cell carcinoma of the cervix.

The patient again refused to continue follow-up. Finally, in August, 1956, she was seen in the Gynecology Outpatient Department and then readmitted to the Hospital. At this time the cervix seemed healed and stained well with iodine. Colposcopic examination was within normal limits (Fig. 1, *D*); cytology smears were classified as Papanicolaou

Class II. After considerable discussion, laparotomy was decided upon. A total abdominal hysterectomy and bilateral salpingo-oophorectomy with dissection of both iliac fossae were performed. Many adhesions were present. One enlarged lymph node was found in the left iliac fossa. In general, however, there was no gross evidence of carcinoma. The pathology reports were as follows: Chronic cystic cervicitis with focal atypical hyperlasia and focal foreign-body granulomatous inflammation, no evidence of carcinoma; late proliferative endometrium; myometrial hypertrophy; chronic nonspecific salpingitis, bilateral, with left hydrosalpinx; small parovarian cyst; multiple follicle cysts of ovaries; reticulum hyperplasia of iliac lymph node.

At present the patient is doing well. Pelvic findings are within the limits of normal. Vaginal cytologic smears have been negative. The vaginal vault is normal by gross inspection and by colposcopy. There is minimal pelvic induration.

Comment

It is well known that inflammation may lead to atypical cervical epithelial changes histologically and cytologically. As squamous epithelium becomes abnormal, glycolysis increases.[4, 5] This explains its lack of iodine staining by the Schiller iodine test. Reagan[6] reports that with histopathological alterations of the cervix, not necessarily in the presence of inflammation, the rete pegs become broad and blunt. This would, incidentally, explain the mosaic pattern of leukoplakia seen by the colposcope.[7] Local antibiotic therapy has been recommended as a form of treatment in some cases of atypism and in preinvasive carcinoma.[8] Without treatment of carcinoma in situ, regression of epithelial abnormalities found by biopsy[9, 10] and by smear[10, 11, 12] has been reported. Regression of abnormal colposcopic findings[13, 14] is also known to occur.

What makes this particular case unique is that we were able to follow, with the subsidence of pelvic inflammation a return to normal, then a reversion to abnormal of (1) exfoliated cells by cytology, (2) epithelial configuration and thickening by colposcopy, and (3) one aspect of cervical epithelial physiology (glycolysis) by iodine-staining with the Schiller test. All three showed a pattern of correlation and parallelism that, in our opinion, deserves reporting in the literature. It is granted that biopsy at the time of the pelvic abscess would have been very desirable; this was not performed because of the danger of spreading the infectious process. Biopsies taken after the pelvic abscess were normal; after another episode of inflammation they showed a lesion variously described by different pathologists. The removed specimen showed no malignancy but this in itself does not prove that a neoplastic lesion was not previously present.

Summary

A case report of unusual cervical changes in a nonpregnant multiparous Negro woman is presented. With two episodes of pelvic inflammation, cytologic, colposcopic, and iodine-staining findings became abnormal, with normal findings in between the two episodes and after the last one. Biopsy subsequent to the second pelvic inflammation showed a lesion variously diagnosed

from severe atypism to early invasive carcinoma. On thorough study of the operative specimen no malignancy was found. The implications of these findings are discussed.

We wish to thank Dr. John B. Montgomery, Professor of Obstetrics and Gynecology, for his encouragement and for his permission to report this case.

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FIBROID OF THE CERVICAL STUMP

Report of a Case

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(From St. Francis Hospital)

GILES, in 1923, contributed the first instance of a fibroid developing in the cervical stump remaining after hysterectomy. Discussing the case, Dr. Herbert Spencer prophetically remarked that fibroids occur far less frequently in cervical stumps than malignancies. A scant 9 additional cases have been reported during the subsequent interval. Concern for benign growths in the abandoned cervix is extensively championed in the works of Collins, and Crawford, who emphasize the symptom potentialities of this surgical orphan. This paper covers an additional instance of a fibroid arising from a cervical stump and requiring operation for relief of symptoms.

Fig. 1.

The patient, aged 47 years, was first seen in October, 1955, complaining of backache, dyschezia, dyspareunia, and loss of an unknown amount of weight over a year's time. She gave a history of a hysterectomy in 1947, at which time, she was told, "everything was removed excepting the ovaries." Married for 21 years, she had never been pregnant, and had undergone no other surgery. Pelvic examination disclosed a cervical stump, normal in appearance, to which was attached a globular mass approximately 4 to 6 cm. in diameter, smooth, and regular in outline. Bimanual palpation of the mass and/or motion of the cervix

elicited exquisite tenderness. On Oct. 12, 1955, the abdomen was entered through the incision of the previous operation. The tumor mass was found to arise from the midpoint of the top of the cervical stump. The round and infundibulopelvic ligaments had apparently been sutured to the cervical stump at hysterectomy, *but no evidence of ovaries could be found.* The cervix and attached mass were dissected free and removed en bloc.

The pathologist's report was: *Gross:* The specimen consisted of a cervix with attached tissue measuring 6.5 cm. in length by 3.5 cm. in diameter. Attached to the proximal end of the cervix was a bulbous tumor which measured 4 cm. in diameter. On cut section the cervical tissue was seen to measure approximately 3.5 cm. in length and the tumor was seen to be composed of homogeneous, white, firm tissue surrounded by a capsule 0.2 cm. in thickness (Fig. 1). *Microscopic:* The tumor had an outer capsule of concentric collagen bands. There was no infiltration of this outer capsule. The inner mass was made up of very cellular intertwining bundles of nonstriated muscle. The nuclei were closely packed and large, but there was complete uniformity of the staining and the chromatin distribution. There was no pleomorphism. The rest of the cervix showed a thin, flat squamous mucosa covering dilated glands. The endocervical columnar cells covered papillary projections. There was infiltration of the upper levels with lymphocytes. *Diagnosis:* Cervical stump, leiomyoma. Chronic cystic cervicitis.

The patient's convalescence was unremarkable, and in the ensuing 6 months she has continued to be relieved of all her symptoms.

This case is added to 10 previously reported to minimize further the innocuousness of abandoning the cervix in the pelvis without so much as an ovary to account for pathologic changes causing symptoms.

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EVALUATION OF METHODS FOR OBTAINING CERVICAL SMEARS FOR CYTOLOGY AND THE INTRODUCTION OF AN IMPROVED SCRAPER FOR OBTAINING SURFACE CELLS

WILLIAM S. HORN, M.D., AND
CHARLES T. ASHWORTH, M.D., FORT WORTH, TEXAS

IN THE past decade exfoliative cytology, as introduced by Papanicolaou, has become an indispensable adjunct in the early detection of cancer, particularly of the cervix uteri. Because the efficacy of these procedures is dependent upon the quality of material made available for cytologic examination, it is desirable to evaluate and improve upon methods that are now in use for obtaining cervical smears.

The procedure for obtaining material from the cervix advocated by Papanicolaou[1] is aspiration from the posterior fornix, the endocervical canal, and, for endometrial cells, from the uterine cavity. Various other procedures are used, but none seems to be flexibly applicable to routine daily use.

For satisfactory cytologic evaluation it is necessary that the material be obtained from the portio, from the squamocolumnar junction, and from the cervical canal. The position of the squamocolumnar junction, therefore, is of primary importance to the obtainment of adequate cytologic material. A study of 26 surgically removed uteri showed that the site of the squamocolumnar junction varied from a point 15 mm. outside the anatomical os on the portio (cases with cervical erosion), to a point 10 mm. above the external os in the cervical canal. There were 10 cases (45.4 per cent) in which the squamocolumnar junction was located in the cervical canal. In at least half of these 10 cases, the squamocolumnar junction was too high to be reached by most methods.

Introduction of an Improved Scraper for Obtaining Cervical Smears

An experience in March, 1955, convinced one of us (W. S. H.) that present methods of taking cervical smears are not uniformly dependable. The patient was a 52-year-old woman who was having some irregular spotting. The cervix had been reported elsewhere as normal in 1950, and again in 1954, but now there was no identifiable portio. A series of slides made of material aspirated from the vagina and cervical canal were negative for tumor cells. Two weeks later, after dilation of the os and cervical canal to size 14 F., a quickly fashioned, arrowlike wooden scraper was introduced 15 to 20 mm., rotated, and adequate material obtained. A preparation of abundant cellular content was the result. It contained predominantly endocervical cells, and in these smears anaplastic squamous epithelial cells were found.

Based on this experience, a new cervical scraper* has been fashioned for more satisfactory ectocervical smears and better endocervical preparations than are obtainable with present commonly used methods. It is presented in the belief that it will effectively improve the quality of material especially from the cervical canal for cytologic study and increase the accuracy of the cytologic method for the detection of cancer of the cervix.

This improved scraper (Fig. 1) has one end for obtaining surface material from the portio, the ectocervical scraper; and the other end, the endocervical scraper, for obtaining material from the cervical canal and from the squamocolumnar junction that is located above the anatomical external os. The ectocervical scraper for the portio has a narrow styloid tip, 2 mm. wide and 5 mm. long, that will fit into the external os as axis of rotation. The scraping surface is 15 mm. wide and fits the curvature of the portio. The tip for making endocervical scrapings is fashioned into a biconcave, arrowlike point 2 mm. wide at the tip, 15 mm. wide at the base, and 22 mm. in length. It will adequately penetrate the endocervical canal, although in some instances a sound will need to precede it for its application to and beyond the squamocolumnar junction.

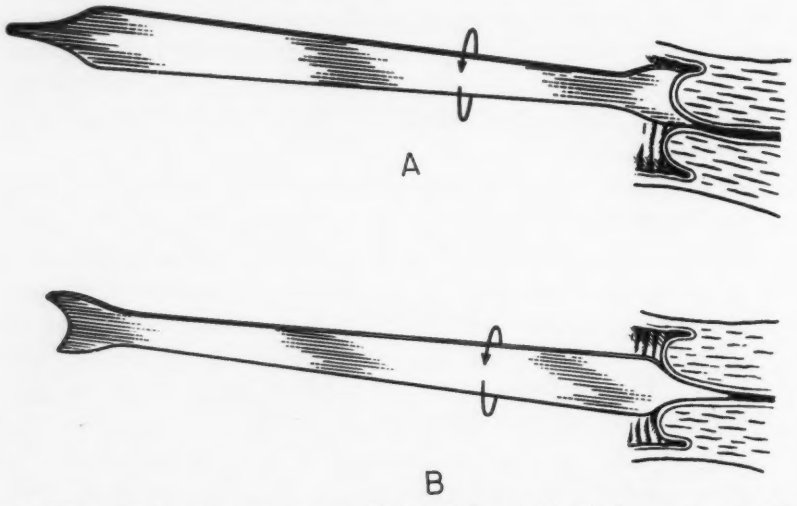

Fig. 1.—*A*, Shows the new scraper as applied to take ectocervical smears. *B*, Shows the new scraper as applied to take endocervical smears.

Comparative Study of Smears Obtained With the Ayre Scraper, the Pipette Aspiration From the Cervical Canal, and the Improved Endo- and Ectocervical Scraper

That cervical material has been obtained from the site of the squamocolumnar junction is indicated by the presence of both endocervical and squamous cells. If no endocervical cells are present in the smears, then it may be assumed that the squamocolumnar junction has not been reached.

A comparative study was made in one group of 23 patients using the Ayre scraper for the first smear and a fresh one for the second. A third smear was then made of pipette-aspirated material from the cervical canal, and, finally, a fourth using material removed with the newly designed endoscraper. These slides were evaluated from the standpoint of total number of cells in the smears, and the degree of representation of squamous cells and of endocervical cells:

1. The Ayre scraper (first slide): 100 per cent of these preparations contained an adequate total of cells for evaluation. Twenty smears (87 per cent) contained squamous cells only, while 3 (13 per cent) contained a few endocervical cells.

*Horn's Cervical Scraper (patent pending), manufactured by Hardwood Products Co., Guilford, Me.

2. The Ayre scraper (second slide): 100 per cent of these preparations contained an adequate number of cells in spite of the fact that the cervix had been scraped for the first slide immediately beforehand. Eighteen of the 23 (78 per cent) contained all squamous cells, 5 (22 per cent) contained predominantly squamous cells with a fair number of endocervical cells.

Fig. 2.

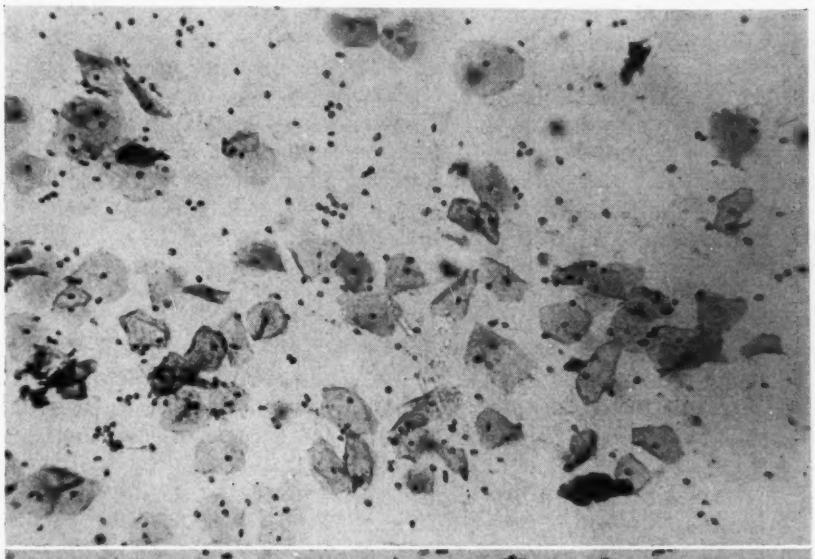

Fig. 3.

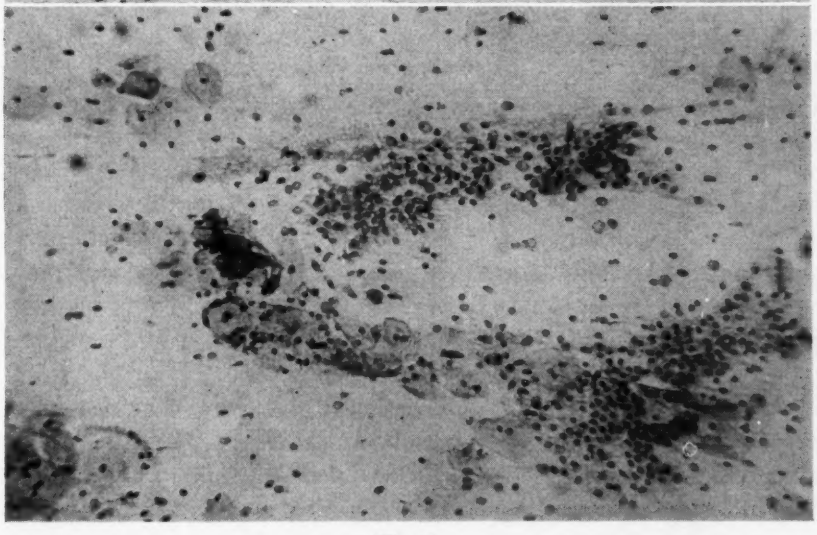

Fig. 2.—Photomicrograph of cervical smear showing all cells to be from portio squamous epithelium. No indication of cell representation from squamocolumnar junction.

Fig. 3.—Photomicrograph of cervical smear obtained with the improved endoscraper. Note admixture of squamous and endocervical cells indicative of representation of the squamocolumnar junction.

3. The pipette aspiration: Of these preparations, 5 (22 per cent) contained only mucus or a few cells, entirely inadequate for evaluation. An additional 4 (18 per cent) were classified as poor or inadequate cell representation. Twelve smears (52 per cent) contained an admixture of squamous and endocervical cells. In this group the mixture was considered to be adequately representative of the lower portion of the cervical canal and the

squamocolumnar junction. In 3 cases (13 per cent) the slides contained only endocervical cells, and in 3 cases (13 per cent) only squamous cells.

4. The new endoscraper: All of these smears contained an adequate cellular content. In 19 of 23 cases (83 per cent) the smears contained a mixture of endocervical and squamous cells. The proportion of endocervical cells was estimated to range from 10 to 90 per cent. In 3 cases (13 per cent) the smears contained all endocervical cells, and in 1 (4 per cent) squamous cells only.

In an additional evaluation study, a series of 27 cases was used in which the portio and external os were sampled with the Ayre scraper. In a second series of 22 cases, the portio and external os were sampled with the improved ectoscraper with the styloid tip applied to the os.

In the series using the Ayre scraper, 6 of the 27, or 22 per cent, were found to contain a few clusters of endocervical cells. In the group in which the improved ectoscraper was used, 8 of the 22, or 36 per cent, contained endocervical cells. This difference is not positively significant. It seems probable, however, from the manner in which the styloid tip can be fitted into the os, that in cases where the cervical squamocolumnar junction is located near the external os, the improved ectoscraper will be superior in obtaining cells representative of the squamocolumnar junction.

From the foregoing study, it is apparent that the most effective sampling of cellular material from the cervix, to include a representation of the portio epithelium, the squamocolumnar junction, and the lower portion of the cervical canal, can be obtained from a surface scrape of the portio, followed by a scrape of the cervical canal with the use of a pointed instrument fashioned as described above. Material aspirated after the use of the endoscraper is uniformly rich in cellular content.

Summary and Conclusions

The most effective application of cervical cytology in the detection of early carcinoma of the cervix is dependent upon a technique that provides an adequate amount of cellular material from the portio of the cervix, the squamocolumnar junction, and the lower portion of the cervical canal. Methods that are presently in use for this procedure do not achieve this result completely, because of the anatomic variability of the squamocoluumnar junction, and because of the nonavailability of an inexpensive expendable instrument designed to enter the cervical canal in an effective manner. A new scraper is presented which fulfills the requirements as we understand them. This scraper has one end to be used as an ectocervical scraper, and the other end fashioned in a pointed, arrowlike manner. The latter will enter the cervical canal and is suitable for obtaining a richly cellular material representative of the lower portion of the cervical canal, and of the squamocolumnar junction in cases where this junction is located above the level of the anatomical os. A comparative evaluation of smears obtained with Horn's improved scraper, the Ayre scraper, and aspiration of the cervical canal by pipette has been made. This study shows superiority of the smears obtained with the improved scraper to the extent that it is believed to be preferred over present methods for routine clinical use in the manner described.

Reference

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A NEW CERVICAL BIOPSY PUNCH FORCEPS

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A NEW cervical biopsy punch forceps* which excises a wedge of tissue at right angles to the surface epithelium is presented. The wedge shape enables the laboratory technician to orient the block of tissue for true cross sections especially across the squamocolumnar junction.

In the search for carcinoma in situ, the ideal cervical biopsy requires the removal of a cone-shaped mass of cervical tissue including the squamocolumnar junction and endocervical canal, up to a few millimeters from the internal os. The cone should be so blocked that good serial cross sections can be obtained. This procedure does not lend itself to routine office, or outpatient department work where selective punch biopsies are required. The new punch forceps has been found useful in securing an adequate piece of tissue across the squamocolumnar junction without cervical dilatation, sutures, or assistants.

The common hemisphere-shaped biopsy forceps has been found fairly adequate but suffers from two defects. It cuts out small bits of tissue which are difficult to orient for proper sectioning; and it frequently is unable to grasp smooth and firm tissue without damaging the specimen.

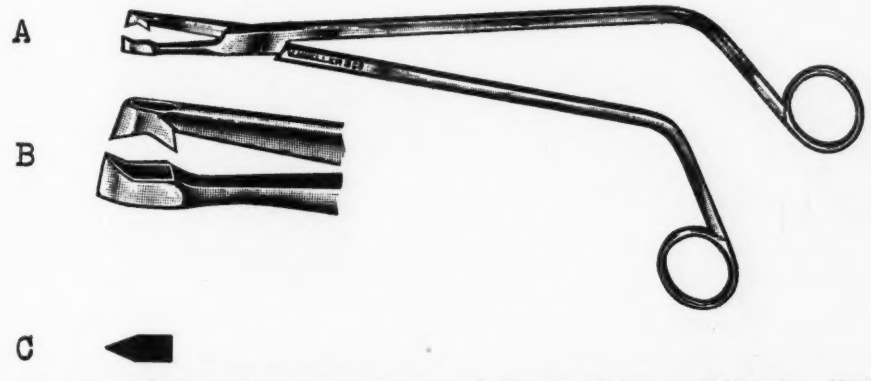

Fig. 1.—A new cervical punch biopsy instrument. *A*, Length of forceps, 10½ inches (26.5 cm.). *B*, Detail of jaws, actual size. *C*, Actual size and shape of bite.

The distinguishing feature of the new forceps is the termination of each jaw in a sharp tooth, not unlike the beaked jaw of a turtle, which grasps and holds the cervix while the upper jaw cuts out the wedge. The nose of the jaw is tapered to a point to produce

*Manufactured by V. Mueller & Company, Chicago, Ill.

a triangular cut with the apex in the submucosal stroma and the widest part of the wedge at the surface. Consequently the deepest part of the biopsy site has the least diameter and bleeding is minimized.

The maximum width of the wedge of tissue obtained by this instrument is 3 mm. It can be slightly narrower and smaller if only the toothed end of the jaw is used. Wedges of tissue varying from 1 by 0.2 by 0.3 cm. to 0.3 by 0.2 by 0.3 cm. can be removed. It is possible to take multiple bites leaving intervening peninsulas of tissue for subsequent biopsies.

To secure best results several points need emphasis. In most cases a Schiller test is recommended to define the squamocolumnar junction. The first few biopsies can be taken while the cervix is held with a tenaculum until one becomes more familiar with the instrument. Even after skill with the instrument is acquired, for greater precision in excising a proper specimen the tenaculum is very helpful.

Several precautions should be followed regarding bleeding after the biopsy. The bites taken at 3 and 9 o'clock when deep healed scars are present should be shallow to avoid bleeding from the cervical branches of the uterine artery which are now closer to the surface. Also, removal of a large wedge may require more careful application of the nasal tip cautery for hemostasis. The ordinary biopsy site is quickly sealed by a quick touch of the cautery tip. There has been no need for hospitalization following this procedure. Packing is rarely used. After six weeks the largest biopsy may leave a barely discernible depressed scar. On only rare occasions does bleeding require recautery of the biopsy site.

A NEW SELF-RETAINING AND SELF-ADJUSTING PATENCY CANNULA*

MELVIN R. COHEN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Michael Reese Hospital)

IN THE past few decades, the investigation of infertile matings has received tremendous impetus. Many more women are consulting physicians regarding this problem than ever before, and, as diagnostic techniques are being evolved, new instruments are being developed to aid in diagnosis.

A complete survey of the infertile female must include the Rubin test for tubal patency. In many instances, hysterosalpingography and pneumoperitoneum are also indicated. We have developed a new cannula to be used in these tests which we feel is superior to many which are now available.

Our instrument is completely adjustable to the size, shape, and position of the uterus. It is leakproof because of the constant pressure exerted by the acorn against the cervical os. In addition, it meets all the other criteria for a successful patency cannula, such as: (1) The instrument should be simple in construction, sturdy, but light in weight. (2) It should be easily cleansed and sterilized. (3) It must be adjustable to the size and position of the uterus. (4) It must fit snugly against the cervix to prevent leakage of gas or radiopaque media. (5) It should be self-retaining so that the physician's hands are free.

Our new instrument has been constructed with all of the above criteria in mind. It is 10½ inches long and made of brass, chrome plated. The tip, which is perforated and malleable, can vary in length from ¾ to 1¾ inches by adjusting the screw collar. This cannula can also be obtained with a flexible spring tip which some physicians prefer for the Rubin patency test. A standard soft-rubber acorn-shaped tip fits snugly against the cervix. The self-retaining clamp fits securely against the lock of the 7 inch single tenaculm forceps by compressing the stainless steel spring on the shaft of the cannula. This spring exerts pressure so that the rubber acorn makes constant contact with the external cervical os, thus preventing leakage. A set screw is provided to fix the clamp to the cannula shaft should the cannula be used without the steel spring. There is a Luer tip at the end of the cannula, with a detachable stopcock also fitted with a Luer tip, should fractional Lipiodol studies be desired.

The technique which we employ, utilizing this cannula, is as follows (Fig. 1):

1. A Graves speculum, modified by having only one arm, is inserted into the vagina, exposing the cervix.

2. The cervix is cleansed with an antiseptic solution and the anterior lip grasped with the 7 inch single tenaculum forceps.

*Presented at a meeting of the Chicago Gynecological Society, Dec. 21, 1956.

3. A uterine sound is used to determine the length and direction of the cervical canal.

4. The cannula is adjusted so that the tip will project just within the internal os.

5. The cannula is inserted and locked in place by compressing the spring.

6. The modified Graves speculum is then removed without disturbing the self-retaining patency cannula.

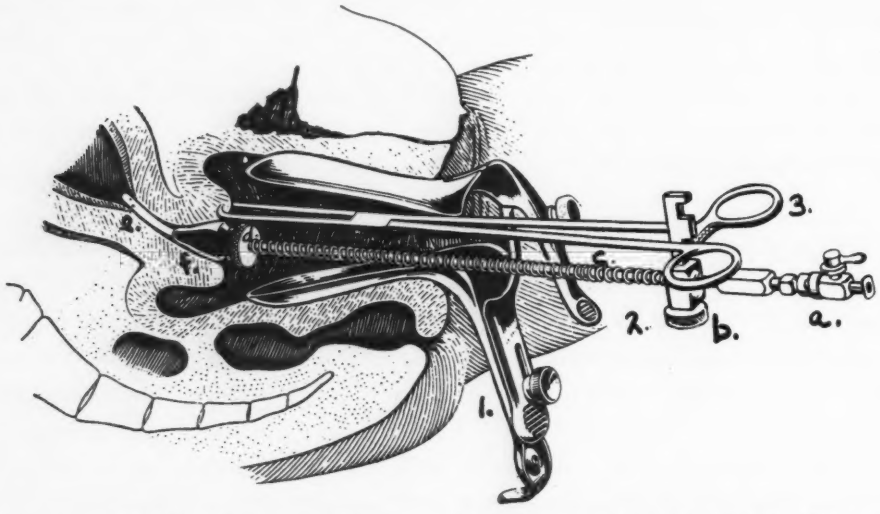

Fig. 1.—*1*, Modified Graves speculum. *2*, Cannula: *a*, stopcock (detachable); *b*, self-retaining clamp and set screw; *c*, spring; *d*, adjustable collar; *e*, perforated tip; *f*, acorn (rubber). *3*, Tenaculum.

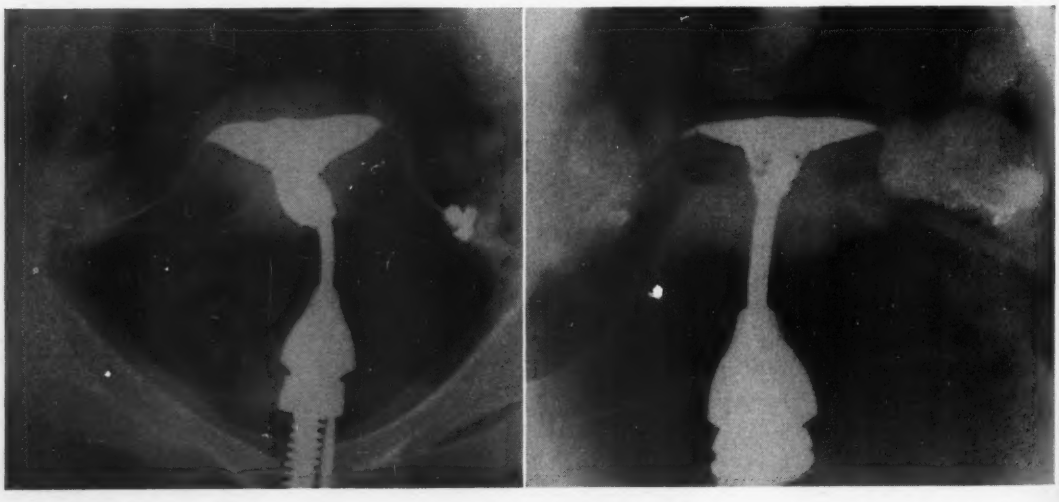

Fig. 2.—Normal pneumoperitoneum combined with iodized oil (complete gynecography).

This new cannula has been used for simple Rubin patency tests and for hysterosalpingography. It has also been found satisfactory for pneumoperitoneum alone or combined with hysterosalpingography (complete gynecography[1]). With the spring exerting constant pressure, one is assured of a tight fit between the rubber tip and the external cervical os. Leak of radiopaque materials has not occurred even when the patient's position has been changed from lithotomy to modified knee-chest and back to lithotomy position, as is necessary in the performance of gynecography (Fig. 2).

In summary, we have described a new patency cannula*† which is leakproof, adjustable, and self-retaining. It has been found completely satisfactory for the performance of the Rubin patency test, hysterosalpingography and gynecography.

References

1. Stein, I. F., and Arens, R. A.: J. A. M. A. 87: 1299, 1926.
2. Stein, I. F., and Arens, R. A.: AM. J. OBST. & GYNEC. 15: 707, 1928.

*This instrument is manufactured by Marco and Son, 246 Fifth Avenue, New York 1, N. Y.

†Some features of the instrument described by Stein[2] have been incorporated in this cannula.

AN IMPROVED VAGINAL HYSTERECTOMY CLAMP*

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(From the Department of Obstetrics and Gynecology, College of Medicine, University of Illinois)

A CLAMP† designed specifically for use in a vaginal hysterectomy operation is presented.

Fig. 1.—Shows the double curve of the forceps. Both end forceps demonstrate the upward curve while the middle one indicates the lateral curve.

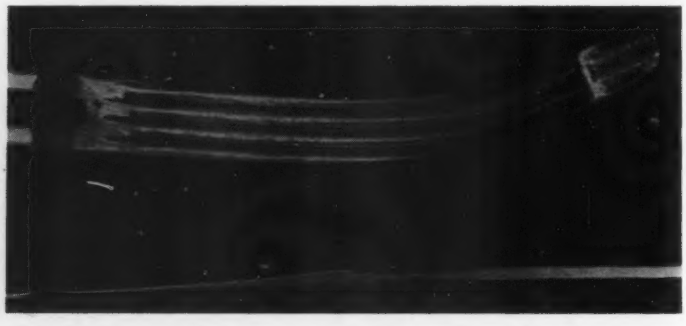

Fig. 2.—Upper portion shows the deep longitudinal ridges and the lock at the right in the forceps blade.

Below is a lateral cross view of the grasped tissue showing how the ridges and furrows have formed. As a result there is little or no likelihood of anything slipping through the forceps.

*Presented at a meeting of the Chicago Gynecological Society, Dec. 21, 1956.

†This clamp is manufactured by V. Mueller & Co., 340 South Honore St., Chicago 12, Ill.

It has not only a lateral curve but also an upward one, incorporated in it (Fig. 1). This greatly facilitates the grasping of tissues as the uterus is progressively freed in an upward direction. For example, reaching up for the uterosacral ligament prior to cutting is simplified and reaching for the top of the uterine supports before cutting loose from the uterus laterally is facilitated.

To increase the value of this instrument, the ridges in the jaws have been placed in long vertical rows as in a Carmalt forceps. This strengthens the grasp of the tissue. Since deep furrows are made, there is no likelihood of the tissues slipping through laterally, for they are held firmly while the clamp is in place (Fig. 2).

In the operation two such clamps are required, on the left and the right, so that they can point both inward and upward on each side. To simplify the handling quickly and accurately by both the surgical nurse and the surgeon, one half of the finger ring portion is colored gold. If this part is always kept down in handling, one can tell quickly and easily whether the clamp is to be used on the right or the left side of the uterus.

Use of this instrument actually shortens the operating time of a vaginal hysterectomy because of the simple, quick, and accurate placing of the clamps, as well as increases the definite security of each bite of the tissue.

Obstetrics

PRESSURES IN THE HUMAN AMNIOTIC FLUID AND INTERVILLOUS SPACE

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(From the State University of New York College of Medicine at New York City and the Kings County Hospital)

THE effective blood pressure in the placenta has been said to be the difference between the pressure of the arterial blood entering the uterus and the intrauterine pressure.[6] Because of the seeming inaccessibility of the intervillous space in the woman these pressure differentials have not been studied. However, recent anatomical studies of Ramsey[5] suggest that the course of the veins draining the intervillous space is such that closure must occur when the pressure on the placenta exceeds the venous pressure at the decidual plate. This fact creates a more complicated situation than previously envisioned. With closure of the placental drainage the intervillous blood pressure will vary in the direction of the intrauterine pressure, but not necessarily at the same speed nor to the same degree, being also influenced by uterine arterial pressure and the tissue resistance of the placenta.

The recent realization that the human intervillous space, particularly the subchorial lake, is readily and safely accessible to needle puncture has made it possible to perform preliminary studies of the relationship of the placental and intrauterine pressures.[2, 3, 4]

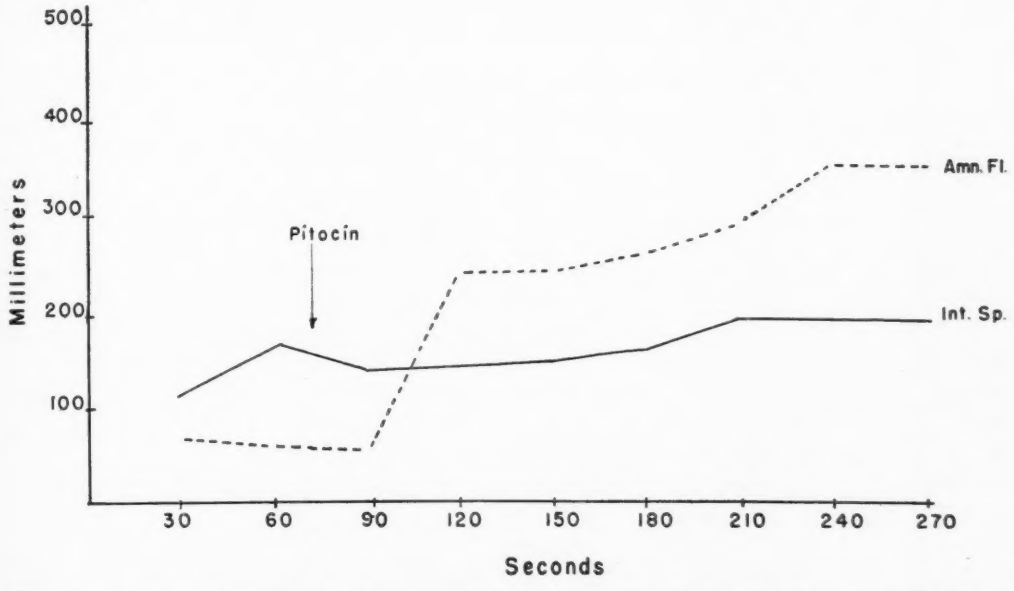
Material and Method

Seven normotensive women at term, delivered by cesarean section, and one who had a therapeutic abortion for psychiatric reasons were studied at the time

of laparotomy. In all of them, the placenta was ascertained to be implanted on the anterior uterine wall by preoperative x-ray, and this was subsequently confirmed at operation.

Pressures were measured by direct reading, glass manometers attached to three-way stopcocks and 19 gauge 1.5 inch needles. The intervillous space was entered by pushing the needle with the manometer attached slowly through the uterine wall until a free flow of blood appeared in the manometer. The free flow at the needle was checked by washing the system with saline and allowing the column of blood to rise again. The amniotic fluid pressure was measured simultaneously by puncturing the uterine cavity with another needle and manometer below the edge of the placenta. Because of the prone position of the patient and the curvature of the uterus, the second manometer was always slightly lower than the first. This difference in height never exceeded 20 mm. and in the majority measured approximately 10 mm. No correction has been made for this in the data to be presented.

The point of reference in this study is the umbilicus. This is approximate because of the conditions surrounding a surgical procedure and because of the effect of the curvature of the uterus previously referred to. In order that this point of reference might be referred to the right ventricle, the umbilicus was determined to be 5.65 ± 1.86 cm. above the sternum in 50 term gravidas of normal size and weight. All pressures were recorded in millimeters of the fluid indicated. In order to ascertain the effects of a uterine contraction, 0.1 ml. of Pitocin was injected intramuscularly in 3 patients after base line pressures had been measured (Figs. 1, 2, 3).



Figs. 1, 2, and 3.—Changes in the pressures of the amniotic fluid and blood of the intervillous space following 0.1 ml. intramuscular Pitocin.

Findings

The Pitocin-induced contractions were not nearly so vigorous as they would have been in the absence of anesthesia. Nevertheless, in one instance (Fig. 2) the pressure of the amniotic fluid exceeded the capacity of the manometer.

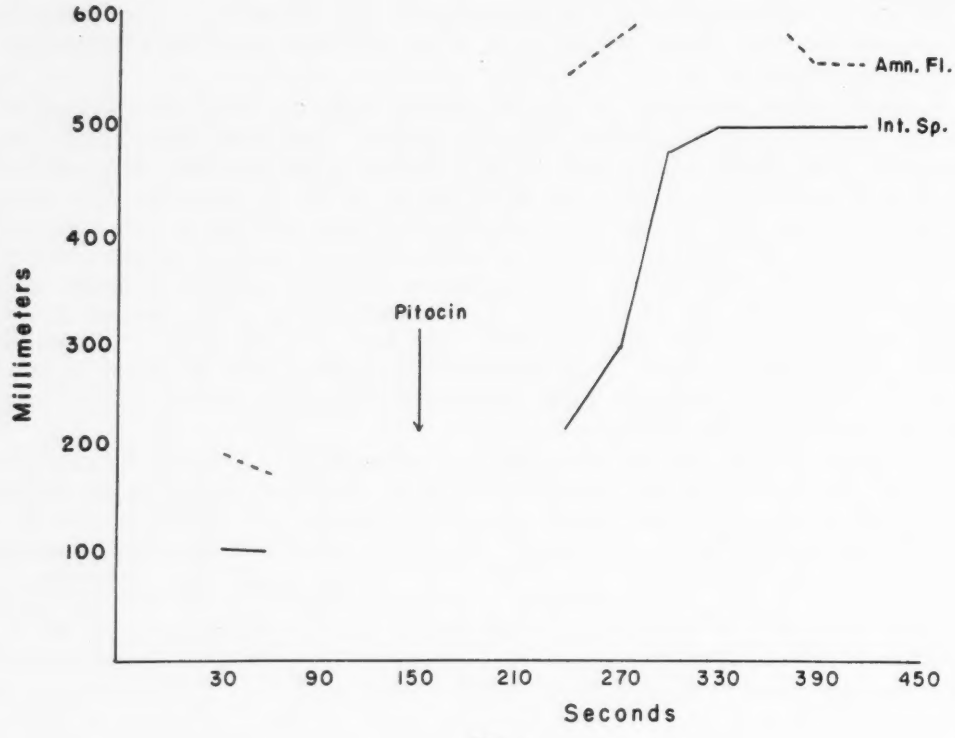

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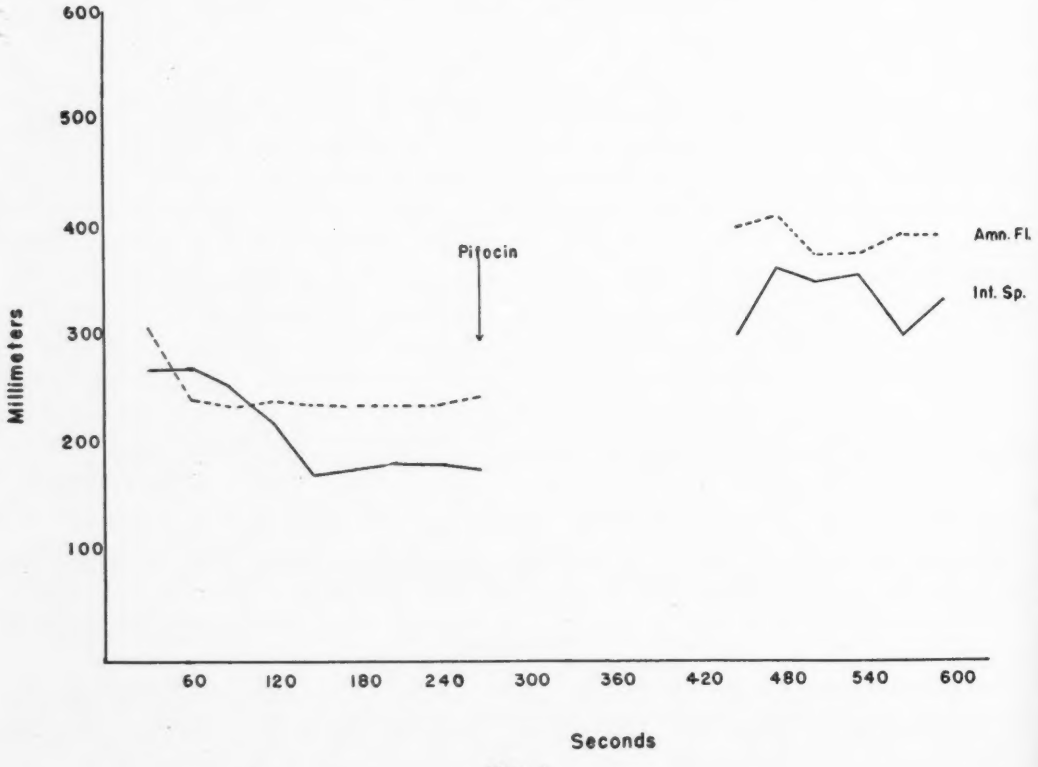
Fig. 2.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Seconds

Fig. 3.

There is considerable variation in the mean resting pressure of both the amniotic fluid and the blood of the intervillous space (Table I). Under the conditions of this experiment there were minute-to-minute changes in the amniotic fluid pressure. Similar instability was described by Alvarez and Caldeyro.[1] The intervillous pressure, on the other hand, appeared more stable, and was less quickly and directly affected by uterine motility. It was surprising how often this latter pressure was less than the amniotic fluid pressure. This must reflect resistance by the placental substance.

TABLE I. PRESSURE IN MILLIMETERS

CASE NO.	AVERAGE RESTING		MAXIMUM AFTER PITOCIN		ANESTHESIA
	INTERVILLOUS BLOOD	AMNIOTIC FLUID	INTERVILLOUS BLOOD	AMNIOTIC FLUID	
1	140	425			Spinal
2	154	120			Spinal
3*	104	195	510	600+	Cyclopropane, ether
4	120	270			Cyclopropane, ether
5	138	68	192	354	Cyclopropane, ether
6	212	247	360	410	Spinal
7	240	205			Spinal
8	265	330			Cyclopropane, ether

*Pregnancy 20 weeks.

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THE DYNAMICS OF PROTEIN CHANGES IN THE AMNIOTIC FLUID OF NORMAL AND ABNORMAL RAT EMBRYOS

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IN A previous study, Wirtschafter and Williams[1] reported that the protein composition of amniotic fluid derived from normal rat embryos throughout the gestation period demonstrated a definite electrophoretic pattern. Therefore, it seemed important to determine whether the protein composition of amniotic fluid derived from rat embryos with congenital defects, cleft palate, hare lip, and in various stages of resorption differed from the electrophoretic pattern observed in the normal. The clinical importance of such differences, if observed in human amniotic fluid, could be of inestimable value in differentiating between a normal and an abnormal fetus, and perhaps could determine the presence of congenital defects and of resorptive processes.

To produce abnormal litters that consist of embroys in various stages of resorption and in which congenital abnormalities like cleft palate and hare lip appear, a diet mixture of the proportion of one part, each, of rat ration and common garden-variety peas (*Lathyrus odoratus*) was fed to normal pregnant rats during the entire gestation period. This diet will hereafter be referred to as the lathyrus diet, and the rat receiving it as the lathyrus-fed rat.

It has been previously shown that no rat embryo can survive in the presence of the lathyrus factor, and that embryos from the same uterus demonstrate a wide range of resorption, from edema of the embryo through resorption of the embryo and finally to complete resorption of the placenta.[2] The weights of embryos being resorbed show wide variation within a litter, as compared to those of normally developing embryos. Resorption in embryos of lathyrus-fed animals can already be detected on the twelfth day after conception.[3] In view of this marked differentiation in the gestation period and in the litters of the lathyrus-fed rat from the normal pattern, it was felt that an electrophoretic study of the amniotic fluid of the lathyrus-fed rat would also show marked variations from the normal. The present study deals with the electrophoretic determinations of the protein composition of amniotic fluid derived from rats fed a lathyrus diet throughout the gestation period.

Methods

Environment.—The experimental animals were housed in an air-conditioned room in which the temperature was regulated at 73 to 75° F. and the relative humidity at 45 to 50 per cent.

Diet.—A mixture of the proportion of one part, each, of the control ration and of peas (*Lathyrus odoratus*) constituted the experimental diet. It was necessary to grind the peas into a fine powder before mixing with the control diet and this 1:1 mixture was made up into hard pellets and utilized as the "experimental pea diet."

Animals.—Twenty-seven adult female rats of the Long-Evans strain were used in this experiment. The day of conception was determined by means of the vaginal smear technique and the time of parturition calculated from this initial finding. Vaginal smears were examined microscopically daily from the time of conception to the day of implantation. Invariably, in normal rats, the presence of red blood cells denoting implantation was observed on the twelfth or thirteenth day of gestation.

Autopsy.—All autopsy procedures were performed with rats under ether anesthesia, and a detailed inspection was made of all viscera. Particular attention was focused upon the uterus. To allow comparative quantitative evaluation of the gestation process, color photographs were made of the uterus, placentas, and embryos, following the removal by cesarean section of the embryos being resorbed. The individual total weight of the embryo was first determined. This weight included the placenta, fetus, amniotic fluid, and the fetal membranes. The amniotic fluid was then removed with a sterile syringe and needle. The weight determinations were made on a Roller-Smith precision balance. However, the older fetuses were weighed on a tension balance.

Electrophoresis.—Paper electrophoresis was performed with a Spinco Model-R apparatus and the stained, dry strips were evaluated with the Spinco Analytrol recording scanner and integrator. Each run was for a period of 20 hours at room temperature (27° C.). Daily electrophoretic determinations were made of the amniotic fluid and maternal serum during the gestation period. For this purpose (1) 60 lambda of amniotic fluid, (2) 60 lambda of amniotic fluid with 5 lambda of maternal rat serum, and (3) 5 lambda of maternal rat serum were placed on Whatman No. 3 MM paper, with a sodium diethylbarbiturate buffer of pH 8.6 and an ionic strength of 0.75. A current of 5 Ma. was employed throughout. It was necessary to utilize a 60 lambda sample because of the low protein concentration of amniotic fluid. To localize and to determine the various protein components of amniotic fluid, 5 lambda of maternal rat serum was added to 60 lambda amniotic fluid samples. For determining the serum protein components, 5 lambda of maternal rat serum was utilized. In this manner, the total protein, albumin, and the globulin components of amniotic fluid could be determined for each day of gestation from the fourteenth to the twentieth day.

Results

Amniotic fluid can be obtained from pea-fed rats in sufficient amount for electrophoretic determination from the fourteenth to the twentieth day of the gestation period. Electrophoretic determinations for the twenty-first and twenty-second days cannot be recorded because of the disappearance of amniotic fluid during the remaining two days of gestation. A comparison of the weights of embryos of litters of normal and pea-fed rats indicates the intensity of the resorptive process in the pea-fed rats. It is evident then that amniotic fluid cannot be obtained from embryos in a marked state of resorption (Fig. 1).

The values for total proteins of rat amniotic fluid during each successive day of the gestation period of normal-fed and pea-fed rats reveal only minor variations until the eighteenth day of gestation. The total protein of amniotic

fluid being resorbed on the eighteenth day shows a marked increase over the normal, and this increase progresses through the nineteenth and twentieth days. Thus, on the twentieth day of gestation, the normal amniotic fluid contains 200 mg. of total proteins per 100 c.c. of amniotic fluid, whereas the amniotic fluid derived from embryos being resorbed contains 745 mg. of total protein per 100 c.c. of amniotic fluid (Fig. 2).

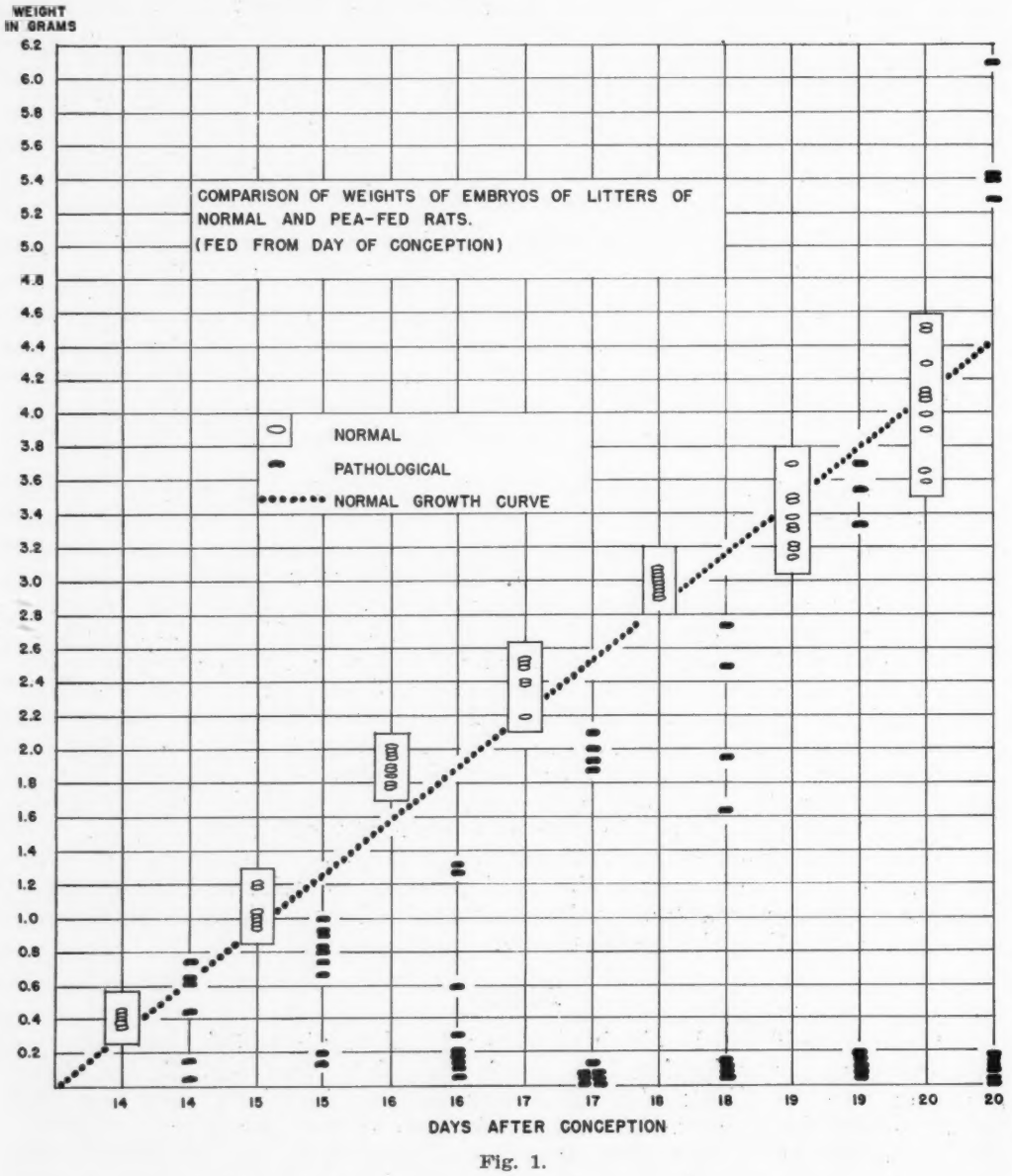

Fig. 1.

The albumin component of amniotic fluid in process of resorption is threefold the normal value on the eighteenth day. On the twentieth day, it contains 233 mg. of albumin per 100 c.c. of amniotic fluid in contradistinction to the normal amniotic fluid, which contains only 75 mg. of albumin per 100 c.c. of amniotic fluid (Fig. 3).

The values for the total globulins of normal amniotic fluid and that being resorbed do not differ until the eighteenth day of gestation. The latter, from the eighteenth to the twentieth day of gestation, contains fourfold the concentration found in normal amniotic fluid. There is little, if any, difference in the concentration of A_1 and A_2 globulin in resorbing and normal amniotic

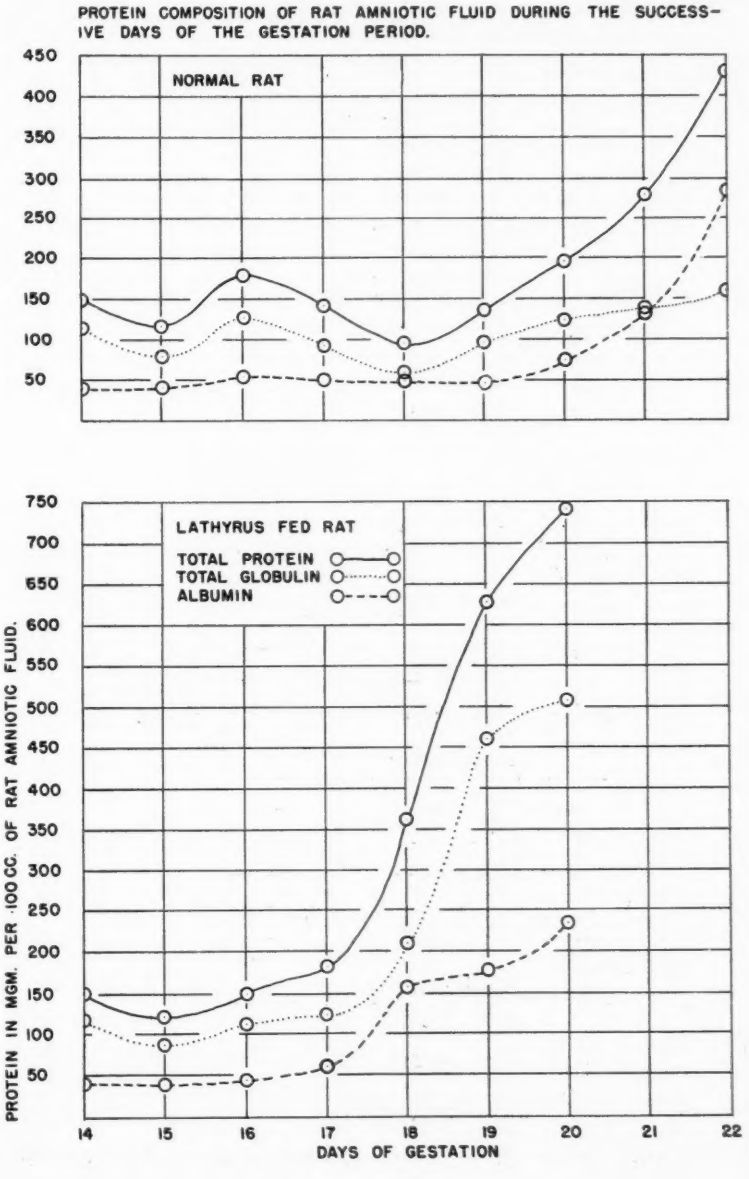
PROTEIN COMPOSITION OF RAT AMNIOTIC FLUID DURING THE SUCCESSIVE DAYS OF THE GESTATION PERIOD.
NORMAL RAT
LATHYRUS FED RAT
TOTAL PROTEIN
TOTAL GLOBULIN
ALBUMIN
PROTEIN IN MGM. PER 100 CC. OF RAT AMNIOTIC FLUID.
DAYS OF GESTATION

Fig. 2.

fluid during each successive day of gestation. However, a marked increase in the beta globulin component is observed in resorbing amniotic fluid from the eighteenth day and, similarly, a marked increase in the gamma globulin during the same period. This increase in the beta globulin is greater than the increase in the gamma globulin (Fig. 4).

The increase in the total protein concentration of amniotic fluid being resorbed is due, therefore, chiefly to the increase in beta globulin and gamma globulin, and to a much lesser extent to the increase in albumin which occurs from the eighteenth to the twentieth day of gestation.

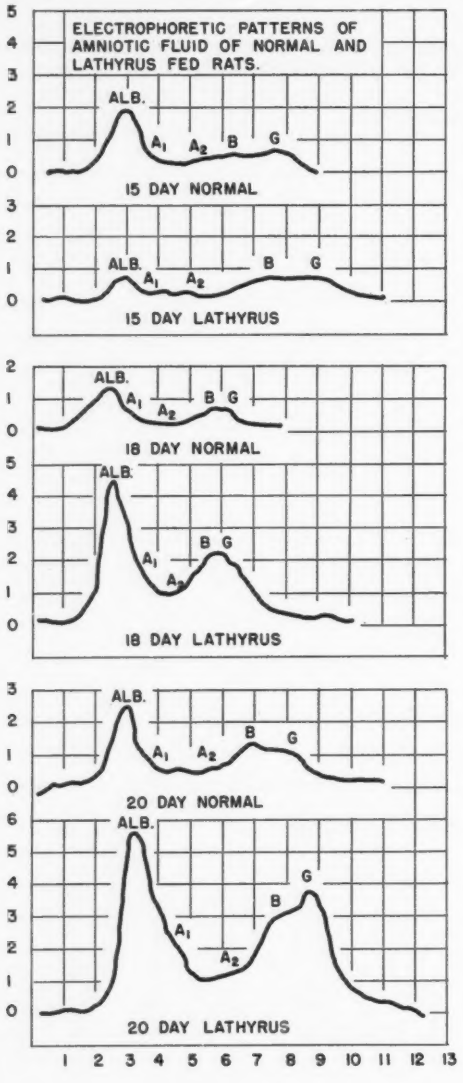

Fig. 3.

Comment

A search of the literature does not reveal any observations on the protein composition of the amniotic fluid in the pea-fed rat during the course of gestation. To observe and study it would be to note an increasing concentration of globulins, particularly from the eighteenth day until the twentieth day of gestation. This increase parallels the intensity of the resorptive process occurring in the uterus of the pea-fed rat. Therefore, on the twentieth day, the resorptive process has proceeded to the point where amniotic fluid is no

longer available in quantities sufficient for protein determinations, in contrast to the normal state. It is to be emphasized, however, that, at the point where these are last obtainable, the globulin curve markedly exceeds the albumin curve, in contrast to their respective curves in the normal rat amniotic fluid at term. A study of the albumin present in the amniotic fluid of the pea-fed rat shows that it does not differ in concentration from that of the normal to any marked degree until the seventeenth day. From then on it exhibits a marked increase and, what is particularly noteworthy, the increase in albumin occurs four days earlier than in the normal rat amniotic fluid.

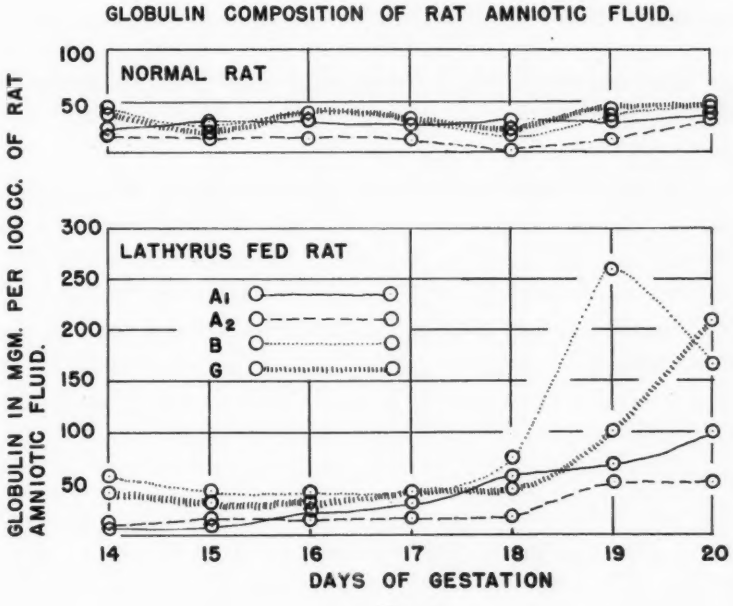

Fig. 4.

These protein increases in the amniotic fluid raise questions of great significance as to their source. Since the globulin of the albumin-globulin ratio of the amniotic fluid is many times greater than the globulin of the albumin-globulin ratio of the maternal rat serum, it is evident that this globulin is not a dialysate. Neither can it be a transudate or an exudate.

Our knowledge of the synthesis of the various plasma proteins is still incomplete. We do know, however, that the synthesis of beta and gamma globulin is attributed to extrahepatic sources and particularly to reticuloendothelial elements. The most important components of the beta globulin fraction are Ac globulin, isoagglutinins, and amylase. The gamma globulin fraction contains some identified and some unidentified antibodies.

This extrahepatic synthesis of proteins that compose the amniotic fluid in process of resorption may then be due to the synthesis of these proteins by the placenta. In both the normal and the abnormal amniotic fluids studied, there is this fluctuating (or differentiated) albumin-globulin ratio as compared to that of the maternal rat serum. The normal shows the greater increase in

albumin; the abnormal the greater increase in globulin. In both, however, the source of the protein increment must be sought in an extrahepatic or placental elaboration.

Since human amniotic fluid is readily available, it is suggested that the dynamics of the protein changes in the amniotic fluid of both the normal and the abnormal human fetus be investigated by this method. Perhaps normal human amniotic fluid will also show a greater increase of albumin at parturition, and abnormal human amniotic fluid will perhaps show a greater increase in the globulin fraction at parturition. Further, studies in the human might help to elucidate even the source of the protein increment.

Summary

1. Amniotic fluid from resorbing embryos of rats on a pea-pellet diet contains a much higher concentration of total proteins than amniotic fluid from normal control-fed rats.

2. Although there is little difference in the total globulins of normal and resorbing amniotic fluid until the eighteenth day of gestation, the resorbing amniotic fluid from the eighteenth to the twentieth day of the gestation period contains fourfold the concentration of globulins found in normal amniotic fluid.

3. The concentration of A_1 and A_2 globulin varies very little in normal and resorbing amniotic fluid during each successive day of gestation.

4. A marked increase of the beta globulin component is observed in resorbing amniotic fluid from the eighteenth day on, together with a marked increase in the gamma globulin.

5. This study of amniotic fluid demonstrates that normal amniotic fluid at the termination of gestation is characterized by an increase in the concentration of albumin, whereas amniotic fluid derived from embryos being resorbed is characterized by an increase in the concentration of globulin, particularly beta and gamma globulin. These findings suggest an application to human material to ascertain if the same reversal obtains, and this problem is now under active observation in this laboratory.

We wish to thank Mr. Dean C. Altman, the head of the Photographic Department of this Hospital, for preparing the graphs, as well as Miss Irene M. Fawcett and Mr. Jimmy K. Tsujimura of our staff for their technical assistance.

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THE PATHOLOGIC PHYSIOLOGY OF THE CLOTTING MECHANISM IN ECLAMPSIA

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SCHAUTA[1] was probably the first (1881) to note the hemorrhagic manifestations of eclampsia. In a detailed analysis of patients who died from this condition over a 45 year period, he described hemorrhagic lesions in various areas of the brain. Five years later Jürgens[2] described the characteristic hepatic lesions and suggested that they were diagnostic of eclampsia. He also noted the hemorrhages elsewhere in the body and referred to hyaline-appearing masses in capillaries. Schmorl,[3] in 1893, probably more than any other person, felt that eclampsia was a generalized vascular disease whose most characteristic manifestation was capillary hemorrhage throughout the body. He emphasized the hemorrhagic aspects of eclampsia and supported his concept with carefully studied and extensive autopsy material. He also noted emboli in small capillaries and suggested the placenta as a place of origin for these emboli because a few contained large dark-staining cells. Welch,[4] reporting to the alumni of the Sloane Hospital in 1908, reviewed this aspect of eclampsia and expressed the following views: "Most of these cases show considerable hemolysis. The masses described as fibrin in the hemorrhages of the liver do not appear as clear cut fibrin fibrils, but have a hyaline appearance which in places appears like fused red blood cell stromas. One finds also in places within the vessels agglutinated red cells which also fuse into hyaline-appearing masses." He did not feel that this process could be explained simply as a phenomenon of embolization, but rather that changes occurred within the vascular bed similar to those resulting from bacterial infection. In this latter condition the red blood cells tend to become spherical, agglutinate, and finally hemolyze. Hyaline thrombi were also commonly found. Sheehan,[5] with the most extensive autopsy experience in pregnancy complications in recent years, feels that the majority of hepatic lesions occur during the last day or so of life and that the autopsy must be carried out within one hour of the patient's death to obtain the characteristic pathologic picture. By this criterion, the characteristic periportal

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hemorrhagic lesions of the liver will be found in 90 per cent of the patients. Dieckmann[6] felt such lesions are not necessarily pathognomonic of eclampsia but rather are limited to patients pregnant or in the immediate puerperium.

The so-called characteristic kidney lesions of eclampsia are also equally controversial. The cortex is pale and the medulla congested. The glomerulus is enlarged, with thickening of the afferent arteriolar endothelium in the glomerular stalk by "fibrils." Hyaline thrombi are present in the capillaries and hemoglobin and red blood casts are noted in the tubules. With vascular disease and abruptio placentae the lesion is primarily necrosis from arteriolar spasm and anoxia. Sheehan feels the lesions found in eclampsia may be due to intermittent arteriolar spasm.

The lungs are congested and petechial hemorrhages are noted throughout the lung substance. There is usually a moderate amount of serous pleural fluid. Hemorrhages are present beneath the endocardium and are associated with small areas of necrosis elsewhere in the myocardium. These hemorrhagic manifestations are found in areas of the brain and meninges and vary in size from microscopic lesions to extensive intracerebral hemorrhages which occasionally rupture into the ventricles. The incidence of brain involvement varies from 20 per cent (Dieckmann[6]) to a high of 90 per cent (Schmorl).

Placental infarcts and subplacental hemorrhages have been discussed by Young,[7] Bartholomew,[8] and Kellogg,[9] both as a cause of eclampsia and as a pathologic lesion associated with it. Young and Bartholomew concurred that the characteristic lesion is primarily thrombosis of the maternal veins with infarction of the adjacent placentas. Bartholomew attributed the formation of the thrombi to spasm of these veins from renal and posterior pituitary factors. Kellogg stated, "Couvelaire uterus occurs typically in so-called toxic separation but also in severe preeclampsia–eclampsia without separation." The adrenals have been described in sporadic cases. The usual lesion is hemorrhage and necrosis of the parenchyma.

Dieckmann remarked that capillary hemorrhages and thromboses are the usual lesions found in other organs.

That a coagulation defect may be present to explain these hemorrhagic manifestations was not formally considered until Stahnke[10] reported the platelet counts in a series of patients with varying degrees of toxemia of pregnancy. In those with eclampsia, he noted a persistent reduction in the platelets to the degree that hemorrhage was an accompanying feature. Others have noted the high fibrinogen in eclampsia.

A defect in the coagulation mechanism was not postulated as a possible causative mechanism of eclampsia until Schneider[11] attributed the "fibrin" emboli to an infusion of a thromboplastic substance from the placental bed into the maternal venous sinuses and embolization of this particulate matter to small vessels throughout the body. Pritchard and associates,[12] studying the hematologic phenomena in eclampsia, determined erythrocyte fragility and noted an increased fragility of these cells. This seems to account for the hemoglobinemia noted in eclampsia by many investigators.

In order to determine any possible role which the coagulation mechanism may have in the pathogenesis of lesions found in eclampsia, the case reports of 6 patients with eclampsia are herewith reviewed. The summaries are presented with emphasis upon the coagulation data and their relation to the clinical course, particularly the presence of arteriolar constriction and urine output.

CASE 1.—V. B.* (U. of P., No. 37936), a 25-year-old Negro, gravida i, para 0, was admitted on May 17, 1950, in the thirty-third week of pregnancy, with the complaint of a severe headache which had been recurrent for a week and was associated with nausea. Her past history revealed that she had been in the University Hospital on two previous occasions, one in 1946 for cellulitis of the left side of the neck, and the other 2 years later for a ruptured tubal pregnancy. The hemoglobin on the first admission was 46 per cent. Hematologic consultation and study had shown only a slight tendency toward sickling on one preparation. The anemia was attributed to the cellulitis, and she received two blood transfusions. She was first seen in the eleventh week of this pregnancy and there was normal progression of the pregnancy on seven subsequent visits. On her last visit 7 days prior to admission there had been a 2½ pound weight loss and the blood pressure had risen from a previous level of 90/54 to 118/92. Laboratory data obtained during the course of her outpatient visits showed a hemoglobin of 63 per cent, a positive Rh factor, and a negative Wassermann test and chest x-ray.

Physical examination disclosed an overtly agitated Negro woman with a blood pressure of 240/140, pulse rate of 88, and respirations 22 per minute. The funduscopic examination made several hours later showed marked spasm of the retinal arteries without evidence of hemorrhages or exudates. On abdominal examination, the uterus was the size of a 33 weeks' gestation and fetal heart sounds were normal. Examination of the extremities showed 2 plus edema up to the mid-leg area and hyperactive reflexes. The urine contained 3 plus protein and numerous red blood cells. Twelve hours after admission, the coagulation factors were investigated because of extensive capillary bleeding. The prothrombin time was 68 ± 13, bleeding time was greater than 29 minutes, clotting time in glass 20 minutes in the third tube, and no clot retraction was noted after 2 hours. There were 28,000 platelets. A bone marrow examination revealed an excess of megakaryocytes without evidence of toxic depression of the other cellular elements, which were seen in normal amounts. The megakaryocytes observed were immature. There were 4 promyelocytes and 8 metamyelocytes in the peripheral smear. The sickling test was not diagnostic, but there was a slight tendency of some of the cells to sickle. The blood was examined at the Philadelphia Serum Exchange for abnormal red blood cell agglutinins and none were found. The bilirubin was 1 mg. per cent in one minute and 4 mg. per cent total.

Clinical Course.—She progressed from oliguria to anuria in the first 3 hours with a total urinary excretion of 310 c.c. During this time she had increasing evidence of petechial involvement with grossly bloody urine and bleeding from the gums. She received 25 Gm. of salt-free serum albumin 8 hours after admission which effected a good diuresis. The pulse pressure became very narrow following this and it became apparent that she was having central nervous system bleeding. This was manifested by increasing coma and signs of a left hemiparesis. A second albumin infusion was given 22 hours after admission without producing a diuresis. The blood pressure began to fall shortly thereafter, and she died undelivered, 31 hours after admission, on May 18, 1950.

Postmortem examination of the mother showed sickled red blood cells clumped in the right internal carotid artery, in the portal vein, and hepatic arteries. The liver sinusoids were filled with hemolyzed blood. The adrenal sinusoids and renal vessels contained sickled

*This case was presented briefly before the Tri-City Obstetrical Society, April, 1951.

erythrocytes. The erythrocytes and normoblasts were sickled in the bone marrow. There were petechial hemorrhages in the brain, submucosal hemorrhages of the gastrointestinal tract, bladder, and ureteral pelvis. There were parenchymatous hemorrhages and necrosis of the liver and adrenals. Postmortem examination of the infant showed petechial hemorrhages compatible with asphyxia. These were found in the thymus, epicardium, lung, kidney, and testes.

Summary.—We have graphically presented in Fig. 1 her clinical course during the 31 hours in which we attempted to reverse the renal failure. We were able to obtain a temporary diuresis with the salt-free serum albumin, but it was not maintained, nor could

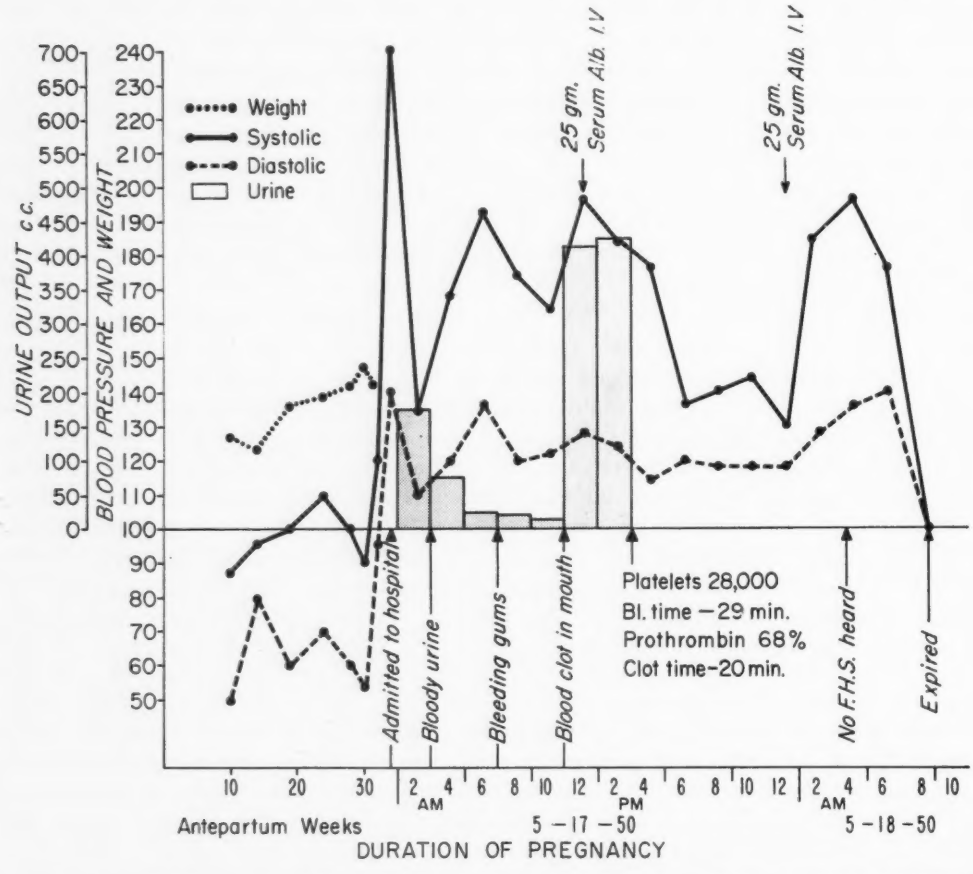

Fig. 1.—Graphic presentation of Case 1. V. B. (U. of P. No. 37936). After the initial dip in diastolic pressure which was accompanied by some urine flow the arteriolar constriction became unerring and by degree ominous. Two attempts were made to return fluid to the intravascular compartment with albumin and effect a diuresis. The first was successful but in the repeat attempt we succeeded only in overloading the vasculature and collapse followed 24 hours of profound peripheral anoxia.

we obtain a diuretic effect from a second 25 Gm. The blood pressure response following this second infusion may have been due to inability of the heart to cope with the additional blood volume. A general diagnosis of sicklemia was made. This had not been demonstrated on several previous occasions and suggests that patients with the trait, as may be the case in this instance, may have a sickle-cell crisis under the proper circumstances. This patient developed severe arteriolar constriction and renal failure, which produced peripheral anoxia resulting in hemostatic defects and hemorrhages throughout the body. The anoxia and pooling probably caused the sickling. The cerebral hemorrhage was probably the immediate cause of death. Hemolysis was quite marked in this case.

CASE 2.—S. H.* (U. of P., No. 39718), a 42-year-old Negro woman, gravida v, para iv, was first seen in the outpatient department in the thirty-fifth week of pregnancy. Her history disclosed that she had had an elevation of blood pressure and seizures following the first delivery. The subsequent pregnancies terminated in normal, full-term, spontaneous deliveries. Physical examination showed a blood pressure of 194/110 and confirmed a normal intrauterine gestation compatible in size with the period of amenorrhea. There was edema of the abdominal wall and 3 plus edema of the legs. She had gained 30 pounds during this pregnancy. She refused to be admitted to the hospital and was given ammonium chloride and asked to report again in 24 hours in the hope that admission could be obtained.

She was seen again one week later and her family reported that she had been sick since leaving the clinic. She had felt very tired, had recurrent headaches and backaches, and for the last 48 hours had been confined to bed unable to sleep. On the morning of admission she had vomited blood-tinged material numerous times. She was admitted in coma on Jan. 11, 1951. Physical examination showed an acutely ill Negro woman who had muscular twitching, sonorous breathing, and generalized edema, especially of the eyelids and face. The blood pressure was 210/110, pulse 60, and respiration 24 per minute. She could be made to follow the hand or a light but could not speak distinctly. The funduscopic examination showed normal-appearing discs with marked attentuation of the arteries. No hemorrhages or exudates were noted. Abdominal examination showed a near-term fetus and the fetal heart sounds were heard. On neurologic examination, the reflexes in the extremities were found to be 3 plus. The coagulation data appear in Table I. The urine contained 4 plus albumin and a few red blood cells but no hemoglobin or bilirubin.

Clinical Course.—After immediate sedation, an attempt was made to deliver her by conservative means. During the ensuing 8 hours her clinical condition deteriorated for she became anuric, developed ptosis of the left eyelid, and required intubation for respiratory exchange. Seventy-five cubic centimeters of urine was excreted during this period and the platelet count was 46,000. She was then given a high spinal anesthesic for the elevated blood pressure. There was an immediate platelet increase following this procedure. An opportune time was thus provided to empty the uterus and this was carried out. The postpartum course was protracted and significant from several viewpoints. Since we are interested here in renal function and hemostatic phenomena, they will be given to explain the data in Table I. Repeated funduscopic examinations showed multiple flame-shaped hemorrhages and a few small fluffy exudates. She remained comatose and showed neurologic and electroencephalographic evidence of a left anterior cerebral mass lesion which was interpreted as an intracerebral hemorrhage. This was manifested by right hemiparesis, disorientation, confusion, and aphasia, which cleared spontaneously three weeks following delivery. A sternal marrow examination performed 5 hours after admission revealed a toxic depression of the cellular elements with a slight increase of megakaryocytes. Her kidney function responded rather slowly. In the 12 hours following delivery, she excreted 156 c.c. of grossly bloody urine and in the subsequent 24 hour period she excreted 1,240 c.c. Thereafter, the volume returned to normal and the hematuria subsided. There was gradual resolution of the hemorrhages noted on funduscopic examination. She was discharged on Feb. 7, 1951. When seen in 6 weeks for follow-up, she complained of being tired and having visual difficulty. The blood pressure at this time was 155/95 and her weight 158 pounds, which was her stated prepregnancy weight.

Summary.—This patient, because of her reluctance to enter the hospital, developed an extreme degree of anoxia from arteriolar constriction and had resultant hemostatic defects throughout her body. Notable was the apparent platelet response to the high spinal anesthetic which enabled us to operate upon her, and more notable was the fortunate outcome with such widespread involvement. As may be noted in Table I she had a further

*This case was presented briefly before the Residents Division of the American Academy of Obstetrics and Gynecology, Philadelphia, Pa., May, 1955.

TABLE I. THE COAGULATION DATA ON CASES 2, 3, AND 4 WITH A RÉSUMÉ OF THE CLINICAL EVIDENCE OF BLEEDING

	HOUR AFTER ADMITTANCE	PLATELETS (PER C.MM.)	OIL CLOT RETRACTION (MINUTES)	PROTHROMBIN SERUM (%)	PROTHROMBIN PLASMA (%)	AC-GLOBULIN (%)	BLEEDING TIME (MINUTES)	CLINICAL BLEEDING
S. H., No. 39718. Severe Eclampsia.—								
	0	,000	75	80	85	95	33	Petechiae 3+, uterine 1+, gums 3+
		Membranes artificially ruptured						
	3	40,000	75	90			35	
		Pitocin infusion started						
	7	46,000	75	90	95		18	
		Spinal anesthesia						
	8	88,000	67	100	100	100	10	
		Cesarean section, marked oozing noted						
	12	54,000	72	100	100	80	8	Gums 1+, uterine 1+, hematuria, retinal hemorrhage, cerebral hemorrhage
	24	92,000	60	70	75	95	5	
	48	202,000	46	60	97	100	4	
	72	294,000	31	30	100	100	1	
F. S., No. 43405. Severe Eclampsia.—								
	7	90,000	63	75	85	100	15	Hematuria
		Continuous spinal anesthesia						
	8	94,000	65					Hematuria
		Cesarean section, moderate oozing noted						
	10	164,000	50	80	90		8	
	23	84,000	65	70			20	
	24	42,000	75	70	75	90		Abdominal wound 3+
	30	48,000	75	50	55	60	24	Abdominal wound 3+
	50	60,000	70	70	70	70	20	
	75	102,000	60	75	95	95	10	
	100	146,000	49	60	100	100	5	0
	125	384,000	21	10	100		3	0
M. B., No. 39683. Hypertension and Eclampsia.—								
	12	58,000		75	100		41	
	14	64,000						Hematuria
		Delivered of a 2,450 gram stillborn infant under caudal anesthesia						
	30	52,000					16	
	78	180,000					7	Retinal hemorrhage
	102	194,000					5	
	150	325,000						

platelet depression when the anesthetic was discontinued and the arteriolar constriction returned. Her urinary output gave evidence of some arteriolar relaxation as it increased progressively in the ensuing 24 hours.

CASE 3.—F. S.* (U. of P., No. 43405), a 29-year-old white gravida iv, para i, was admitted on March 31, 1952, in the thirty-third week of pregnancy. She had awakened feeling irritable and restless on the morning of admission and had complained of a severe headache. She subsequently developed severe epigastric distress and vomited several times. The family reported that she had a generalized convulsion at 9:00 A.M. and another 2 hours later. She was having a third while being admitted at 1:00 P.M. The 2 previous pregnancies had ended in an abortion at 8 weeks and a miscarriage at 26 weeks, respectively. She had been seen five times in prenatal clinic with a normal blood pressure and no edema. The last blood pressure reading 3 weeks prior to admission was 112/74. She had gained 21 pounds with this pregnancy. Physical examination showed a severely ill patient having a generalized convulsive seizure. The blood pressure was 220/150. Funduscopic examination showed severe spasm of the retinal arteries, but no hemorrhages or exudates. Breathing was labored and irregular. There was a sinus tachycardia of 110. Abdominal examination disclosed that the size of the uterus was compatible with the period of amenorrhea. The fetal heart tones were present and normal. Neurological examination showed hyperactive reflexes and a bilateral Babinski sign. There was 2 plus pitting edema of both legs. The urine contained 4 plus protein and many red blood cells.

Clinical Course.—She had a fourth convulsion 5 hours after admission and the fifth 7 hours after admission. Following this last convulsion she was given a spinal anesthetic by catheter and was delivered by cesarean section of a 1,360 gram infant. She excreted no urine prior to the cesarean section, but in the following 12 hours, while the blood pressure was being controlled with the catheter spinal, she excreted 200 c.c. The urinary volume and platelets gradually increased in the subsequent 24 hour periods. The total urine volume was 670 c.c. on the second postpartum day and 1,980 c.c. on the third postpartum day. The urine continued to show 3 plus protein and many red blood cells and casts. Her subsequent hospital course was uneventful and she was discharged on April 9, 1952.

Summary.—This patient was admitted with severe arteriolar constriction, anoxia, and associated renal failure. In the presence of continued convulsive seizures and renal failure it was felt advisable to empty the uterus and this was carried out with a spinal anesthetic, which also served as a hypotensive agent. When the blood pressure was maintained at a lower level with the spinal, the urinary output and platelets responded temporarily. When this method of therapy was discontinued, the arteriolar constriction returned and she had a final convulsion. It will be noted in Table I that the platelets decreased and the abdominal wound began to ooze with the reversal of her clinical course following removal of the spinal anesthetic.

CASE 4.—M. B. (U. of P., No. 39683), a 33-year-old Negro gravida iii, para i, who had had one abortion, was admitted on Jan. 5, 1951, in the thirty-third week of pregnancy. She had been nauseated and had vomited numerous times during the preceding 5 days and had a severe headache with photophobia during the previous 24 hours. Her first pregnancy had ended with severe pre-eclampsia. She and her mother had essential hypertension. Her prenatal care had consisted of nine visits with a weight gain of 27 pounds. There was no significant change in the blood pressure, which had remained at approximately 130/96, until the last visit. At this time the blood pressure had risen to 148/108 and there was a trace of proteinuria. She appeared for admission 5 days later. Physical examination disclosed a dyspneic, acutely ill Negro woman with generalized edema. The blood pressure was 210/110 and the pulse was 140 per minute. She had gained 8 pounds in the previous week. Besides

*Grateful acknowledgment is made to Dr. Harry Fields, for permission to present this case and Case 5.

the obvious edema of the face and hands, she had 3 plus pretibial edema. There was a Grade II hypertensive retinopathy on funduscopic examination. Examination of the chest revealed numerous râles over the bases compatible with pulmonary edema.

Clinical Course.—She had a generalized convulsion following admission and became progressively oliguric. In the first 5 hours she excreted only 160 c.c. of grossly bloody urine that contained 4 plus protein. The membranes were then ruptured artificially and she was given a caudal anesthetic to lower the blood pressure. She responded to these procedures and the urine output increased to 50 c.c. per hour. A repeat funduscopic examination showed two small flame-shaped hemorrhages along the inferior temporal artery on the left retina. The fetal heart sounds had been normal through this period but shortly before the delivery, which occurred 18 hours after admission, they could not be heard. She delivered a 2,450 gram stillborn infant without any abnormal bleeding. Her subsequent hospital course was not remarkable, for she excreted a total of 6,000 c.c. of urine in the 24 hour period following delivery and the blood pressure returned to the predelivery level of 140/90. She was discharged on Jan. 14, 1951, and was seen for a follow-up examination 8 weeks later. The blood pressure at this time was 144/94 and her weight had returned to its prepregnancy level of 136 pounds. Postmortem examination of the infant showed diffuse medullary hemorrhage of both kidneys and subarachnoid and subdural hemorrhage over most of the cerebrum. These pathologic lesions were described as being characteristic of anoxic anoxia.

Summary.—This patient had hypertensive vascular disease when she became pregnant and during the latter part of pregnancy developed severe pre-eclampsia-eclampsia. The additional arteriolar constriction resulted in some degree of anoxia with hemostatic defects which were evident by the presence of hematuria and hemorrhages in the retina. The coagulation data are given in Table I. The infant exhibited hemostatic defects which are quite similar to those seen in eclampsia but in the case of the infant they are attributed to anoxic anoxia.

CASE 5.—I. G. (U. of P., No. 41596), a 36-year-old white gravida i, para 0, was admitted on Aug. 19, 1951, in the twenty-sixth week of pregnancy, with a history of ankle swelling for the previous 4 days and the development of lower abdominal and back pain during the previous 36 hours. She had developed a severe headache 8 hours prior to admission, which was associated with severe nausea and vomiting. Her prenatal care had consisted of four visits with a weight gain of 13 pounds. The blood pressure had not varied significantly from 116/72 on these visits. On the admission physical examination, she was somewhat unresponsive and the blood pressure was 220/115, the pulse 48, and respirations 14 per minute. Her eyes moved independently of each other. Examination of the heart and lungs was negative. The size of the uterus was compatible with the period of amenorrhea and the fetal heart sounds were not heard. There was a 2 plus pitting edema of both extremities. The hematocrit was 51 per cent.

Clinical Course.—Shortly after admission, she was catheterized and 2 c.c. of bloody fluid obtained. Approximately 25 minutes following admission she became unresponsive and progressively developed coma and respiratory obstruction requiring intubation. The funduscopic examination made on admission showed several hemorrhages and an elevation of the disc margins with arteriolar narrowing and irregularity. The electrocardiogram showed a diffuse, nonspecific myocardial abnormality. The prothrombin time was 43 ± 17 and there were 146,000 platelets. The coma became progressively deeper and 25 Gm. of salt-free serum albumin was given for the anuria without effect. On further blood studies gross hemolysis was evident and the total bilirubin was 3.4 mg. per cent. The serum potassium at this time was 8.5 meq. per liter, presumably due to the intravascular hemolysis. A repeat platelet count, carried out one hour after admission, showed 90,000 platelets. Five hours after admission she was delivered of an 810 gram stillborn fetus. Her clinical condition slowly deteriorated and with peripheral vascular collapse she became unresponsive and died 21 hours after admission, on Aug. 20, 1951.

Postmortem examination revealed subendocardial hemorrhages of the heart, subcapsular hemorrhages of the liver, and fibrinoid thrombi in the portal vein. Around its smaller branches were small petechial hemorrhages. There were extensive subserosal hemorrhages of the gastrointestinal tract and bladder and a basilar subarachnoid hemorrhage confined to the cisterna.

Summary.—With the onset of severe arteriolar constriction this patient became acutely anuric. As these two conditions persisted, hemostatic defects became evident and progressed. Eventually potassium and the heme pigments were released by the hemolysis to aggravate the toxemia, and the vascular tree became unresponsive because of peripheral anoxia and basal compression from the bleeding.

CASE 6.—C. H. (KCH No. 333702), a 29-year-old Japanese gravida iv, para i, who had had 2 abortions, was admitted to another hospital at term on Sept. 5, 1955, in active labor with this pregnancy. On admission she was ambulatory, oriented, and complaining only of the uterine contractions. Her prenatal course had been uneventful. The blood pressure determinations were all within normal limits. No protein was found in any of the urine specimens. She had been seen one week prior to admission when the blood pressure was 118/74 and her weight was 2 pounds below her prepregnancy weight. On physical examination on admission the blood pressure was 180/120 and 1 plus ankle edema was noted. Twenty minutes following admission, while expelling an enema unattended, she apparently fell to the floor. When found several minutes later, she was lying beside the bed unconscious. She responded somewhat in the following 30 minutes and complained coherently of the uterine contractions. The blood pressure at this time was 180/120 and the fetal heart sounds were normal. Her condition gradually deteriorated. The right pupil became markedly dilated and she developed a bilateral Babinski sign. The left arm and leg were noted to be flaccid at this time. Six hours following admission, she suddenly stopped breathing and after intubation was delivered by classical cesarean section without anesthesia. Following the cesarean section a lumbar puncture was done which showed blood-tinged spinal fluid. A burr hole was made through the right temporoparietal area without a hematoma being found. She was placed in a respirator and transferred to our hospital for care.

On admission to King County Hospital, the patient was unresponsive, intubated, and in a respirator. The blood pressure was 100/0 and the pulse 108 per minute. She was unresponsive to painful stimuli. Examination of the head revealed the previously noted burr hole. The eyes were fixed, widely dilated, and unresponsive to light. Two hemorrhages were noted in the left retina. The remainder of the physical examination showed the cesarean section scar, 2 plus ankle edema, and a bilateral Babinski sign. No other reflexes were obtainable. The hematocrit was 47 per cent on admission and there were 150,000 platelets. Twenty-four hours later the number of platelets was reduced to 60,000 and at this time the prothrombin was 38 per cent. Her condition slowly deteriorated in the following 12 hours and she excreted only traces of urine. Peripheral vascular collapse followed and the blood pressure was maintained with Levophed. She died twenty-seven hours after admission, on Sept. 6, 1955.

The postmortem examination showed a Y-shaped fracture of the right temporal area with laceration of the middle meningeal artery and resultant subarachnoid hemorrhage. There was a 5 cm. area of discoloration of the brain beneath the left frontotemporal area which was consistent with contrecoup injury. Microscopic sections of the liver showed subscapular hemorrhages and necrosis of liver cells. The kidney sections showed thickening of the glomerular basement membrane which is consistent with eclampsia.

Summary.—This patient, while severely ill with eclampsia, sustained a skull fracture with resultant subarachnoid hemorrhage. It was the opinion of the pathologist that the skull fracture was the precipitating cause of death and that the eclampsia and renal failure were contributory factors. The platelet counts reflected the severe arteriolar constriction and further reduction in their numbers was noted with the use of Levophed.

Comment

In this accumulated experience with eclampsia, it became apparent that an understanding of petechia formation and intravascular thromboembolism was the major requisite for comprehension of the pathologic lesions. The great strides made in our understanding of the factors responsible for containing the blood and maintaining its fluidity have made this review timely, for little explanation could be given for these lesions prior to Krogh's initial observations on the capillaries. These lesions having been interpreted in the light of this accumulated review, several necessary revisions were made in the presently accepted concept of these pathologic features, "for certainly pathology is but an idle pastime unless its ultimate object be to discover means which will prevent the perversion of function which produces lesions and changes."

Moon[13] has written an excellent monograph on the capillary phenomena associated with shock and has drawn heavily upon the work of Landis,[14] who contributed a great deal to our understanding of capillary permeability in relation to arterial and osmotic pressure of the blood. Zweifach,[15, 16] Samuels,[17] and O'Neill[18] have studied the intracellular cement substance and blood supply to the vessel wall for a better understanding of the part these factors play in containing the blood or causing thromboembolism. The factors within the vascular tree which may cause thromboembolism have been reviewed by Lutz,[19] who quoted extensively the observations made by Knisely[20] on sludging.

To review briefly the changes which occur in the capillaries, it is generally stated that they are sensitive to anoxia, abnormal metabolites, light, an acid pH, and changes in temperature. These conditions result in a change in the intracellular cement substance which causes the platelets to stick and pile up in these areas. Fibrin strands are then precipitated out on these platelet clumps. As the process is prolonged and the hydrogen ions increase, leaky areas are evident and clefts appear between the cells. The final result is the extrusion of red cells through the cell wall. Landis and Moon have noted an increase in lymph coming from regions of the body subjected to anoxia which eventually contains platelets, erythrocytes, and granulocytes. With the loss of plasma, the capillaries become packed with red cells and circulatory stasis results. This sequence of events results in serious effusions, increased flow of lymph as noted, hemoconcentration, capillovenous congestion, stasis, and eventual petechial hemorrhages. Animal experiments would thus lend suggestive evidence to explain the increased capillary permeability and the formation of petechiae.

The evidence for "spontaneous" thromboembolism is not nearly so clear, but Lutz stated that the factors generally conceded to be significant in thromboembolism are (1) increased coagulability, (2) relative venous stasis, (3) increased adhesiveness, and (4) injury to the vascular wall. In eclampsia there is a relative increase in the globulin fraction of the plasma due to the selective loss of the smaller-moleculed albumin through the capillaries. This selective filtrate of the plasma proteins which makes up the edema fluid and is contained in the urine has been examined by electrophoresis. The resulting pattern shows some mobility for all the proteins except fibrinogen and the albumin component is disproportionately increased. This loss occurs without lymphatic obstruction or hypo-albuminemia. Prothrombin, convertin, Ac-globulin, and fibrinogen are all globulins. Fibrinogen is the only one of these factors which we definitely know shares in this selective increase and it may reach 600 mg. per cent. Alexander and associates[21] have shown that prothrombin and convertin, like fibrinogen, are increased in normal pregnancy. It does not seem unreasonable to assume that they too may share in the globulin increase and thus reach a higher level in eclampsia. The selective increase of globulin is further accentuated by hemoconcentration.

It is difficult to state definitely that venous stasis does occur but blood flow studies of the kidney[22] and placental bed[23] have shown a decreased flow in severe eclampsia. The only contradiction to its occurrence is the usually quoted work of Munnell[24] on hepatic blood flow. In his determination of hepatic blood flow, using hepatic vein catheterization and Bromsulphalein as the test substance, he studied 6 patients. Three of these had higher blood flow values than those obtained for normal pregnancy. The highest value occurred in a patient who had eclampsia with her first pregnancy and severe pre-eclampsia with the second. This pregnancy, in which the liver blood flow was determined, progressed uneventfully to term and ended with normal labor and delivery. The suggestion that liver blood flow is increased in eclampsia is not justified by these data and Munnell expressed this conclusion.

There is a relative increase in adhesive platelets[25] in pregnancy. These are the so-called "active platelets" or functional platelets which contribute to clotting. There are no reports on studies carried out to determine this quality in the eclamptic patient, but studies carried out in other patients with tissue necrosis have demonstrated increased adhesiveness and we would expect to find this in eclampsia. Additional evidence that the formed elements are seriously affected by severe pre-eclampsia-eclampsia is found in the well-known reports of Knisely and co-workers. Sludging was demonstrated in 22 of 23 pregnant patients[26] with complications and was consistently noted in severe pre-eclampsia. Pritchard[12] and others have shown that the red cells have increased fragility in eclampsia and hemoglobinemia is detected when searched for. These two findings suggest that agglutination and loss of hemoglobin occur. The hemoglobin moiety may pass through the cell wall leaving the stroma or be discharged by disruption with the components fragmented and embolization of this particulate matter.

The evidence for injury to the vascular wall is fairly conclusive when one remembers the extensive and numerous references to this pathologic lesion and the clinical evidence in the form of petechiae and edema. Many authors have also described a proliferative vasculitis[5] and endarteritis.[27] There is, therefore, direct evidence that the vessel wall itself is affected.

The factors Lutz considered to be significant in thromboembolism are present in eclampsia with the reservations noted.

The predilection for the serous cavities and liver may be explained on the basis of Kelan's[28] work. He has demonstrated that the liver and gastrointestinal tract are the major areas of pooling in shock and when absent the organism can withstand increased increments of blood loss. Is it possible to relate this experimental work to the well-known pathologic picture in eclampsia? In the ordinary case of shock due to blood loss, there is arteriolar constriction which pools the remaining blood in the splanchnic area. In severe pre-eclampsia-eclampsia, with the 30 per cent increase in blood volume, the arteriolar constriction must shunt the blood centrally to these splanchnic organ systems. The presence of this increased blood volume may account for the characteristic pathologic lesions noted in eclampsia. The petechiae are primarily in the liver and often submucosally in the gastrointestinal tract and bladder. They may be found in the adrenal and subendocardially when searched for. Possibly significant in this regard are the cases here reported. The patients who died were in the twenty-sixth, thirty-third, and fortieth week of pregnancy. The first two deaths occurred near the time of maximal blood volume increase. The other death resulted from a skull fracture. Of the other patients in this report, 2 were in the thirty-third week of pregnancy and one was in the thirty-fifth week of pregnancy. A factor against the availability of a great deal of blood for pooling is the increase in hematocrit. However, this occurs with the 16 per cent increase in red cell mass which is present in normal pregnancy and

would therefore supply a quantity of packed cells for pooling. A similar situation is present in shock but these individuals do not have the additional red blood cells for pooling.

Central nervous system bleeding may be accounted for by the large amount of antithromboplastin[29] present in this tissue. This material, in the presence of defective thromboplastin formation, which occurs in thrombocytopenia, accounts for many of the deaths from hemophilia and may be the proximate cause of central nervous system bleeding in the eclamptic patient.

There are several points to be considered when these cases are viewed in the light of this discussion. The first is that in these cases there are findings common to shock,[30] anoxia, and death due to severe trauma except in the liver manifestations. The lesions in this organ we attribute to the pooling of a large quantity of blood in this area. This blood is not available in the other conditions and accounts for the so-called characteristic lesions of eclampsia. The second item is the less-than-casual relationship between the severity of the process as evidenced by urinary output and the severity of the thrombocytopenia. As anuria became apparent and progressed the thrombocytopenia became more profound. In Case 3 this apparent correlation was evident. As noted in the protocol the platelets fluctuated as the arteriolar constriction fluctuated, the urinary output varying from anuria to oliguria. The evidence for this is only suggestive. In unpublished work of one of us (W. B.),[31] studies were carried out in patients undergoing surgical procedures to determine the platelet levels when shock ensued. The results, though somewhat inconclusive because of the use of blood transfusions, demonstrated that the immediate response was an increase of the thrombocytes, but with prolongation of shock the platelets were progressively reduced and eventual hemorrhage from no platelets resulted.

Summary

It is not within the scope of this paper to discuss the etiology of eclampsia but certain facts can be repeatedly demonstrated once the patient presents herself with this condition. The first of these is the involvement of small vessels and, because the diastolic pressure is uniformly elevated, we consider the arteriole to be primarily affected. The attenuation of the retinal arteries, presence of edema, and changes in the arterioles of the glomerules further suggest involvement of these vessels.

The sequence of events appears to be as follows: Arteriolar constriction varies in degree and is somewhat selective. Thus minimal degrees of vascular involvement are associated with subtle changes, but tissue anoxia and edema result. When the involvement is extensive and profound, it is associated with severe oliguria or anuria. In this latter instance severe damage from anoxia accrues and may become irreversible. Acidosis results from anoxia at the capillary level. Both these factors affect the intracellular cement substance, and platelets and fibrin adhere to this area of the cell wall. If the process is prolonged, the small-moleculed albumin escapes through clefts between the cells and is followed by the eventual extrusion of cells and the formation of petechiae when the platelets can no longer contain the blood. The profound constriction pools a large quantity of blood in the splanchnic area which accounts for the upper quadrant pain and enlargement of the liver. The hematocrit increases, with loss of the fluid compartment, and this is associated

with a relative increase in the globulin fraction which contains the coagulation factors. Decreased blood flow is associated with this increase and the stage is set for platelet clumping, red blood cell sludging, and agglutination. The eventual result is sequestration of these formed elements. The clotting factors are involved in these small vessel emboli because of the increased coagulability of the blood. The circulating platelets are severely reduced in numbers by this process, and when blood begins to leak out in the central nervous system, it proceeds with abandon and will eventually be the immediate cause of death if not stopped. The progression of this series of events can be immediately reversed by arteriolar relaxation which is clinically manifest by increased urine flow. Other causes of death in eclampsia result from failure of the organism to withstand this process and these include heart failure, rupture of the liver, or a cerebral aneurysm, and abruptio placentae. Death will follow from bleeding if these complications do not occur and the patient remains undelivered and anuric. We concur with Sheehan that the severe liver lesion probably occurs shortly before death and with Dieckmann that it is singular to pregnancy because of the increased blood volume. The presence of "fibrin" thrombi in the small capillaries can be explained on this basis, but the term should be discarded until identification is absolute, for it is extremely misleading to the uninitiated. Vassar,[32] in his review of the platelet thrombosis syndrome which has clinical and pathologic manifestations quite similar to those of eclampsia, vividly describes these hyaline thrombi but attributes them to platelets.

Conclusions

1. The most characteristic feature of eclampsia is the vascular lesion which results in widespread anoxia and increased permeability of the small vessels.

2. This permeability increases selectively the globulin fraction of the blood, causing the blood to be hypercoagulable.

3. Intravascular agglutination of the formed elements with included fibrin produces the small vessel thrombi in severe pre-eclampsia-eclampsia. This occurs because of vessel wall damage, increased adhesiveness, stasis, and hypercoagulability of the blood.

4. These manifestations are not singular to the complications of pregnancy, except in their distribution, but may be found secondarily in a variety of disease entities.

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ANTIHYPERTENSION THERAPY IN TOXEMIA OF PREGNANCY*

A 30 Month Progress Report

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PRIOR to Jan. 1, 1953, the treatment of the hypertensive toxemias of pregnancy on our service had consisted essentially of heavy sedation with morphine, barbiturates, and magnesium sulfate. The effectiveness of this therapy and the difficulties which are secondary to it, such as poor handling of respiratory secretions, the problem of maintaining oral feedings and medication because of semiconsciousness, the diminution of renal output by morphine, and the dangers of heavy sedation to the newborn infant are well known and do not need to be emphasized. From Jan. 1, 1953, to July 1, 1953, a small series treated with Apresoline was amassed. After the latter date, however, a more potent antihypertension drug in toxemias of pregnancy, protoveratrine,† was available to us and we have centered our therapy about this until the present date. The protoveratrine used is a pure alkaloid of *Veratrum album* in a constant ratio of protoveratrine A (2/3) and protoveratrine B (1/3). Actually, to evaluate this drug fully, the first 40 cases were treated without benefit of any sedation—even in labor—except for magnesium sulfate.

Satisfied that this alkaloid is effective and safe orally and parenterally when properly used, and devoid of some of the frequent unpleasant side effects that were evident with the earlier crude combinations of Veratrum alkaloids, we have continued to use this valuable adjunct. Thus, this paper covers a 30 month continuing evaluation of its use on our service.

Material and Methods

The 196 patients studied were ward patients in whom a diagnosis of toxemia of pregnancy had been made. Of this group there were 18 with mild pre-eclampsia, 159 with severe pre-eclampsia, 8 with eclampsia, and 15 hypertensive patients with superimposed pre-eclampsia.

The method of treatment started on admission consisted of the following:

1. Protoveratrine:
   a. Basal medication 0.5 to 1 mg. orally every 2 to 4 hours until the desired responses were obtained; then as indicated for maintenance (usually this was the only medication required in mild pre-eclampsia). The average duration was 7.5 days.

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†Supplied by Sandoz Laboratories.

b. Intravenous medication, 0.1 to 0.5 mg. in 1,000 c.c. 5 per cent dextrose in distilled water, dripping at 30 to 50 drops per minute. If there was no significant response, 1 ampule (0.1 mg.) directly into the infusion tubing, taking 2 minutes for the injection, and repeated as necessary.

2. Apresoline, 20 mg. intravenously when indicated. (This indication is discussed later.)
3. Absolute bed rest.
4. Routine laboratory tests.
5. Fluids orally and intravenously amounting to output plus insensible loss.
6. Salt-free, high-protein diet.
7. Magnesium sulfate, 2 c.c. 50 per cent intramuscularly every 2 hours for four times.
8. Diuretics as necessary.
9. Evacuation of the uterus as indicated by clinical course if labor has not begun during control period.

A more detailed outline of the methods of therapy has been previously reported.[1, 2]

Result and Comment

Since its inception, this method of therapy has been intended to combat the characteristic vasospasm of toxemia of pregnancy and to cause a regression of some of its more prominent manifestations, thus enabling us to deliver these patients with greater safety than when heavy sedation only was used. Indeed, with the marked hypertension present in most cases, cerebral hemorrhage has been a constant threat. Recent evaluation of all maternal deaths at Charity Hospital of Louisiana showed that in 17 of the 36 deaths (47.2 per cent) due to toxemia in the past ten years (1946-1955) cerebrovascular accidents were the immediate cause.[3] None has occurred during this 30 month survey. The basic cause of toxemia may still be active in some cases, however. This is apparent from the continuing increase in blood urea nitrogen and uric acid levels, in spite of the fact that therapy has caused the blood pressure to fall to normal levels, with regression of proteinuria, pathologic findings in the eye grounds, and edema, as previously emphasized. This disease may progress to fetal death although all of these manifestations have regressed. Hence, we have made no effort to carry these patients to term, realizing the fallacy of such an attempt. We have rather delivered them as soon as their condition became stabilized and as soon as the clinical situation permitted maximum safety for mother and fetus. Typical cases are shown in Figs. 1 and 2.

During their hospital stay these patients are alert and able to handle their respiratory secretions adequately while at bed rest, as well as to take oral feeding and medication. Oliguria has not been observed after 24 hours of treatment.

One hundred seventy-seven deliveries were vaginal and 19 (9.6 per cent) were by cesarean section. In the entire series there were 10 sets (5.1 per cent) of twins.

One maternal death (0.51 per cent) occurred following a vaginal delivery.

This patient died 1½ hours post partum. She was admitted to the delivery unit and in labor, received an enema and progress was rapid with delivery at 7:30 P.M. Following delivery, the patient appeared in good condition with blood pressure of 150/80. An infusion of 5 per cent dextrose in distilled water with one ampule of protoveratrine was started. Suddenly the patient had a generalized convulsion and died. An autopsy was

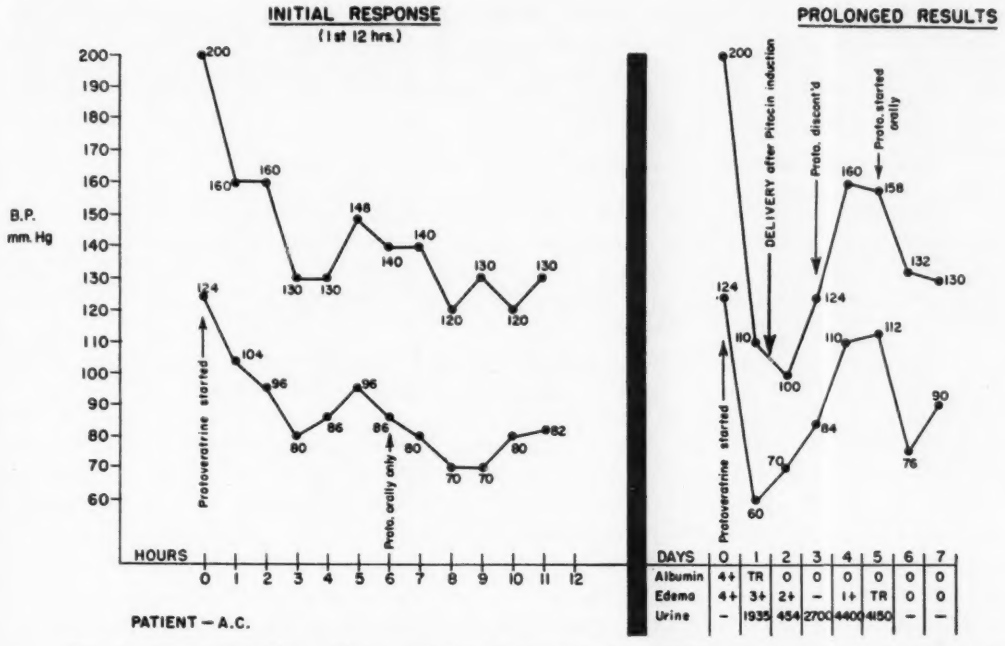

Fig. 1.—Pre-eclampsia. These graphs show the immediate and over-all response in Patient A. C. who received protoveratrine, 0.2 mg. intravenously in 1,000 c.c. of 5 per cent dextrose in water on admission, and 1.0 mg. orally every 4 hours. Pitocin induction approximately 24 hours after control was successful and delivery uneventful. Protoveratrine was discontinued on the third postpartum day but had to be reinstituted on the fifth postpartum day to control still significant hypertension.

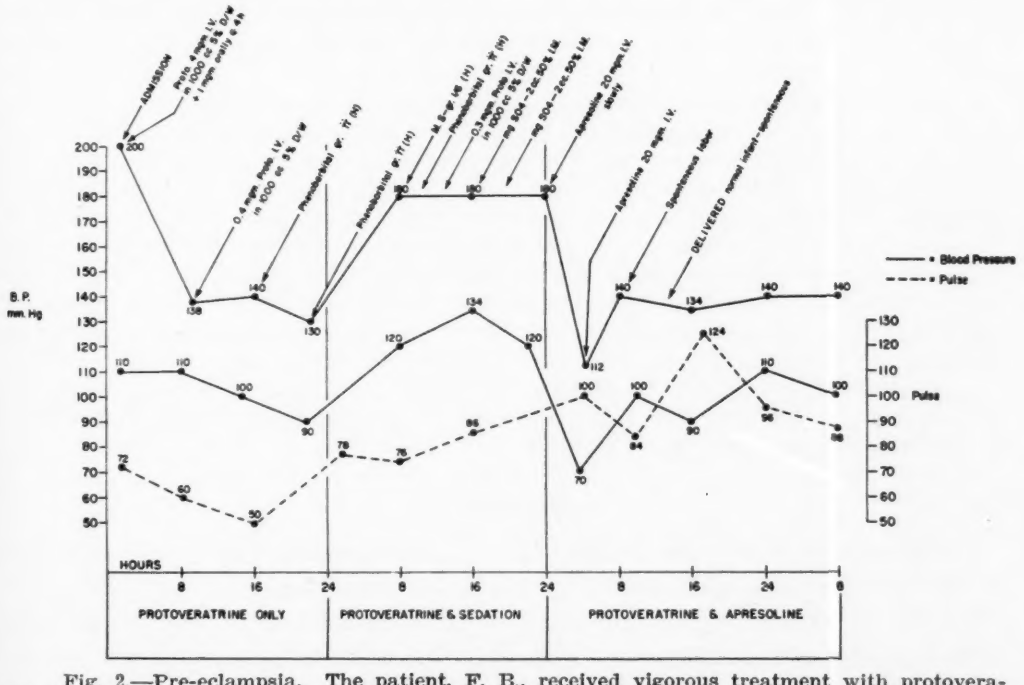

Fig. 2.—Pre-eclampsia. The patient, F. B., received vigorous treatment with protoveratrine intravenously and orally. The initial response was excellent. After this initial response the blood pressure rose to pretreatment levels in spite of sedation. Apresoline, 20 mg. intravenously, decreased the blood pressure to normotensive levels, at which time labor began and a vaginal delivery of a normal infant was accomplished. The postpartum course was uneventful.

performed and no satisfactory evidence could be found for the cause of death. The following are the postmortem diagnosis and findings: (1) cardiac hypertrophy, (2) passive congestion of the liver, (3) pulmonary edema, (4) passive congestion of the lungs, (5) ascites, slight, (6) healed pyelonephritis, minimal, (7) benign nephrosclerosis, slight, (8) leiomyoma of the uterus, (9) toxemia of pregnancy, clinical.

The medication used seemed in no way implicated in her death.

The fetal mortality in these cases of toxemia consisted of 6 (3.0 per cent) stillbirths. Two of these were due to abruptio placentae; no satisfactory reason could be found for the remaining 4 other than toxemia. Three (1.5 per cent) neonatal deaths occurred. Two of these were due to prematurity and to congenital heart disease.

Toxic manifestations were infrequent and usually easily reversible. Vomiting was the most common side reaction, recorded in 36 patients (18 per cent). In several instances, however, it seemed to have causes other than the alkaloid under study. When vomiting was due to protoveratrine, it could be corrected by reducing the total dose or by adjusting the schedule of medication. Atropine also diminished the incidence of vomiting, as did aluminum hydroxide given with protoveratrine.

Bradycardia occurred 17 times (8.5 per cent) and was uniformly corrected by atropine. Hypotension occurred in 4 cases (2 per cent) because of overenthusiastic therapy. This hypotension was corrected by reducing the protoveratrine given or by utilizing a sympathomimetic drug. These patients did not exhibit a classic picture of shock. They were alert and oriented, pulse rate slow and rhythm regular, skin warm, with no dyspnea. A blood pressure between 70 and 90 systolic and between 50 and 40 diastolic was the only finding. The urinary output was not reduced. Tolerance was infrequently encountered in this series but it was here that Apresoline found its greatest usefulness, for, by continuing the protoveratrine medication and adding Apresoline, we were able to obtain a renewed reduction of the blood pressure.

Rather than give a mixture of protoveratrine and Apresoline initially, we have found it more advantageous to give the more effective medication first and keep Apresoline in reserve for patients in whom a further reduction in blood pressure (especially diastolic) may be indicated and those infrequent patients who suddenly develop tolerance. Previous experience has shown that by the addition of Apresoline to the therapy of patients receiving protoveratrine an increase in heart rate is the most constant response, while reduction of the diastolic pressure is the next most frequent occurrence. In 3 instances an elevation of systolic pressure was observed when Apresoline was given in addition to protoveratrine. In these 3 cases, however, when cardiac output was calculated according to Starr's[4] formula, there was a definite increase, and it is believed that this increased cardiac output might explain the relatively insignificant increase in systolic pressure.[2]

Summary

The results of a thirty-month continuing evaluation of protoveratrine and protoveratrine-Apresoline combinations in the treatment of the hypertensive toxemias of pregnancy are recorded. That this method of therapy is safe, effective, and advantageous is apparent. Tolerance to protoveratrine has infrequently been noted, and it is in these patients and those who require a further reduction in blood pressure that Apresoline has found its greatest usefulness.

The complications arising from hypertension have definitely been reduced. The nursing care is markedly simplified. From this large series we have shown that the toxic manifestations of protoveratrine and Apresoline are few and mild.

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1636 LOUISIANA AVENUE.

PROGNOSTIC PRETOXEMIA TEST IN PREGNANCY

Exaggerated Pressor Response to Norepinephrine*

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THE policy of some obstetricians of placing all pregnant patients on a "salt-poor" diet as a matter of routine is theoretically justified in principle as an attempt to forestall possible toxemic complications. In practice, however, it often fails to accomplish its purpose because of two psychological factors: (a) in the realization that a systematic sodium restriction is of vital significance in only a relatively small percentage of cases, while it constitutes a major inconvenience for all, the respective dietary instructions are liable to be given halfheartedly and with less strictness than would be necessary for the benefit of the still unrecognized real toxemia candidates who need them most; (b) the resulting negligence on the part of many patients may be paralleled by an undue confidence on the part of the physician concerning the adequacy of prophylaxis. Thus, medical supervision may not always be sufficient to prevent more or less sudden critical developments.

For this and other reasons of intended prophylactic effectiveness, various attempts have been made in the past to find clinical criteria which would presage the approach of toxemic complications at an early preclinical stage.

Edema, although usually preceding and accompanying toxemia, is too common a phenomenon (occurring in up to two thirds of all otherwise normal pregnancies[1]) to be of prognostic value, and even albuminuria may occur in the absence of other more serious derangements (hypertension, eclampsia).

The recent discovery of an excessive production and urinary excretion of reducing and sodium-retaining steroids of adrenal cortical (and/or placental?) origin,[2-9] preceding and during toxemia, suggests a pathogenic role of these steroids in the toxemia syndrome. Unfortunately, their quantitative assay is too cumbersome for clinical application. Functionally, mineralocorticoid overactivity in pretoxemia and toxemia is manifested by two characteristic features: (a) a diminution of the salivary sodium content[10, 11] which varies too widely to be used as an individual diagnostic criterion, and (b) an exaggerated response to pressor agents such as Pituitrin[12] and norepinephrine,[13, 14] even before the basal pressure has been raised.[13, 15] While Dieckmann's[12] Pituitrin test involves certain hazards according to this author's own statement, we[10] found the intravenous administration of norepinephrine in a dosage of 0.3 mcg. per kilogram

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per minute over a 5 minute period (see below) in over two hundred tests to be free of side effects, except for pallor and occasional slight headache during the infusion. The heart rate is usually slowed by norepinephrine. In patients with congenital heart disease, valvular lesions, arrhythmias, myocarditis, and in those with overt congestive failure, the test should be avoided.

Table I shows the pressor responses of 60 nulliparous young women as controls, compared with those of 100 completely normal pregnant patients with mutually overlapping groups of pregnant patients exhibiting edema and albuminuria, and with 17 pregnant patients who had been normotensive before and at the time of the test but developed hypertensive blood pressure levels (over 140 mm. Hg systolic, over 90 mm. Hg diastolic) subsequently between the test and delivery. With a very few exceptions, all tests were carried out between the twenty-eighth and thirty-sixth weeks of pregnancy.

TABLE I

TYPE OF CASES	NUMBER OF CASES	AVERAGE BASAL BLOOD PRESSURE (MM. Hg)	AVERAGE DEVIATION OF BLOOD PRESSURE DURING NOREPINEPHRINE INFUSION (MM. Hg)	
			SYSTOLIC	DIASTOLIC
Nulliparous controls	60	106/61	+27.6 (±12.3)	+24.1 (± 7.9)
Normal pregnancies*	100	108/60	+29.3 (±12.4)	+21.4 (± 9.5)
Cases with edema†	50	113/67	+40.0 (±20.5)	+23.6 (± 9.5)
Cases with albuminuria†	24	115/70	+41.5 (±26.1)	+21.6 (±10.8)
Cases with subsequent hypertension‡	17	121/74	+50.5 (±29.6)	+23.8 (±11.9)

*No edema, no albuminuria, no hypertension.

†Overlapping groups with edema and/or albuminuria before and/or after the test.

‡Cases with normal blood pressure before and at the time of the test but with hypertension (systolic > 140 mm., diastolic > 90 mm. Hg) between the test and delivery.

Since we[16] had previously found that dietary sodium restriction reduces the pressor effectiveness of norepinephrine, it seems safe to assume that an indefinite number of our normally reacting, but potentially toxemic, test subjects exhibited a normal pressor response because of having been on a more or less strictly salt-poor regimen for some time prior to the test. Furthermore, we felt obliged in the patient's interest to recommend institution or continuance of rigid sodium withdrawal in most instances of marked pressor hyperreaction, thus probably preventing subsequent toxemic manifestations in some of these patients. Despite such inevitable partial ambiguities, there remained a group of 10 maximal hyperreactors (Table II), all of whom presented some abnormalities (albuminuria and/or edema) before and/or after the test. Six became hypertensive after the test (Nos. 1, 2, 3, 8, 9, 10). Three (Nos. 7, 8, 10) became eclamptic. (As far as we know, none of our normal reactors developed eclampsia subsequently.)

TABLE II. PRESSOR RESPONSES OF 10 MAXIMAL HYPERREACTORS TO 0.3 MCG. PER KILOGRAM PER MINUTE OF L-NOREPINEPHRINE, INFUSED INTRAVENOUSLY DURING 5 MINUTES (AVERAGES OF 5 READINGS EACH)

PATIENT NO.	WEEK OF GESTATION	BASAL BLOOD PRESSURE (MM. HG)	DEVIATION OF BLOOD PRESSURE DURING INFUSION OF NOREPINEPHRINE (MM. HG)		EDEMA	ALBUMINURIA	HIGHEST SPONTANEOUS BLOOD PRESSURE AFTER TEST	REMARKS
			SYSTOLIC	DIASTOLIC				
1	34	118/84	+98	+37	+++ after test	-	160/112	(Mother had been toxemic.) Salt-poor after thirty-fourth week
2	33	135/74	+70	+30	+ after test	-	158/95	Salt-poor after twenty-fourth week
3	33	116/66	+61	+22	+++ before and after test	++ after test	146/96	Serpasil and Diamox after twenty-sixth week
4	24	125/65	+55	+23	++ after test	-	135/85	Salt-poor after thirteenth week
5	30	130/80	+62	+33	+ after test	+ after test	130/90	Edema in previous pregnancy
6	33	125/80	+48	+22	+ before and after test	++ after test	125/85	Salt-poor after thirty-seventh week
7	37	112/78	+69	+26	+++ before and after test	++ after test	130/70	Salt-poor after twenty-fourth week. Eclampsia after test
8	31	130/80	+95	+25	+++ after test	++ before and after test	170/130	Salt-poor after thirtieth week. Eclampsia after test
9	31	122/60	+94	+34	+++ before and after test	+ before and after test	146/95	Toxemia in following pregnancy
10	33	120/86	+68	+52	+ before and after test	++++ before and after test	190/110	Toxemia in previous pregnancy. Eclampsia after test
100 normal pregnant patients		106/61	+27.6 (±12.3)	+24.1 (±7.9)				

Of particular interest are 4 hyperreactors (Nos. 1, 2, 4, 5) who were otherwise entirely symptom free and 3 (Nos. 3, 6, 7) who displayed only edema at the time of the test. Without the norepinephrine test, none of these 7 patients

would have been clinically suspected of impending complications. Yet, 3 of them (Nos. 1, 2, 3) became hypertensive; one (No. 7) became eclamptic. In one (No. 4) toxemia had been diagnosed during a preceding pregnancy and one (No. 1, a 21-year-old primipara who developed hypertension after the test) seemed to have a hereditary predisposition. All of her mother's pregnancies had been complicated by toxemia.

In view of the conspicuously close causal relationship of a clear-cut vascular hyperreactivity to norepinephrine as a manifestation of mineralocorticoid overactivity on the one hand, and a tendency toward pretoxemic and toxemic complications on the other, we feel that the norepinephrine infusion test (details below) constitutes a practically useful diagnostic tool for the prediction of impending toxemia and of the necessity for introducing drastic prophylactic measures.

In case the average of the five systolic pressure elevations during the 5 minute infusion exceeds 50 mm. Hg, the suspicion of approaching complications is justified. An average rise of 60 mm. Hg or more makes the danger of impending toxemia appear acute. The behavior of the diastolic pressure is less characteristic and apparently of no definite diagnostic value.

Performance of the norepinephrine test may be considered as especially indicated in otherwise asymptomatic patients if they present marked edema, if they had been toxemic during previous pregnancies, and if there are indications of a hereditary predisposition to toxemia.

In general, there is no advantage in carrying out the test earlier than in the thirtieth week of gestation. While hyperreaction may be interpreted as indicative of approaching trouble, an early normal response does not preclude later complications. (One of our ultimately eclamptic patients had displayed a normal reaction in the thirtieth week but a highly abnormal pressor response in the thirty-seventh week of gestation.) Thus, a repetition of an initially normal test within several weeks will be in order if conditions warrant continued suspicion.

I have no personal experience with Assali's[17] "TEAC blood pressure floor test" (abnormally weak depressor effect of tetraethylammonium chloride) which, although based on a different principle, may offer similar prognostic advantages, and by its addition may increase the conclusiveness of the norepinephrine test.

General Procedure of the Test

Before lying down, the patient should urinate in order to avoid restlessness during the test. A cannula is inserted in a cubital vein connected with a two-way stopcock which in turn is connected with two infusion bottles (see below) hanging on a stand at the bedside. Cannula and stopcock should be anchored to the arm with strips of adhesive tape to permit a steady undisturbed inflow. First, one of the two bottles, containing plain 5 per cent glucose solution, is kept in open connection with the cannula and the solution is permitted to flow through the venoclysis unit (Venopak) at the rate of approximately one drop per second, while on the other arm the blood pressure is being measured repeatedly until it has settled down for at least 10 minutes at a constant minimum level.

Now the connection of the stopcock is switched to the second bottle which contains l-norepinephrine (Levophed*) in 5 per cent glucose, freshly prepared by addition of 1 c.c. of commercial Levophed to 250 c.c. of glucose solution.

While an assistant is carefully adjusting and watching the drop count (determination of the drop count, see below), the blood pressure is noted at the end of each minute until the end of the fifth minute of infusion (five times in all). After this, the cannula can be removed, and the test is ended. The entire procedure requires approximately 30 minutes.

Equipment Needed.—

Blood pressure apparatus; two 250 c.c. infusion bottles with 5 per cent glucose solution and two Venopak venoclysis units; an infusion stand for two bottles; two sterile 18 or 20 gauge cannulas; one sterile two-way stopcock fitting the heads of the cannulas; an electric metronome; Regitine for the merely theoretical case of untoward side effects; one pinchcock with screw which, if attached to the plastic tube connecting the norepinephrine-containing bottle with the stopcock, is to be used for fine adjustment of the drop count during the norepinephrine infusion (the aluminum clamps which come with the Venopak units are too clumsy for accurate flow adjustment); one 10 c.c glass measuring cylinder.

Calculation of Drop Count for Infusion. Detailed Performance of Test.—

The patient must be weighed stripped, or an approximate allowance must be made for clothing. In order to determine the exact number of drops of norepinephrine solution for the desired dosage (0.3 mcg. per kilogram per minute), it is necessary first to calibrate the outflow from the Venopak unit. This is done by using a 10 c.c. measuring cylinder and by letting some of the norepinephrine solution flow into it via the plastic tubing, with a sterile 18 or 20 gauge cannula attached to the latter to protect the open end from being contaminated. One person has to count the drops from the small outlet of the Venopak unit; another person has to watch the filling of the glass cylinder until the level has reached 10 c.c. This indicates the number of drops equaling 10 c.c. It usually varies between 175 and 230 drops. The number of drops needed to give a dosage of 0.3 mcg. per kilogram per minute is calculated according to the following formula:

$$\frac{3 \times \text{number of drops per 10 c.c.} \times \text{number of kilograms of body weight}}{400}$$

The metronome must be set at the figure nearest to the number of drops per minute as figured above.

After this, a sterile cannula is inserted in the vein connected with the sterile two-way stopcock, and the latter is connected with both fluid-filled, air-free plastic tubes, while one bottle of the plain glucose is flowing, and the tubing of the other one remains clamped. Later, during the entire 5 minutes of norepinephrine infusion, the time coincidence of the falling drops with the clicking of the metronome must be kept adjusted as closely as possible by means of the pinchcock screw.

The average blood pressure reaction of the patient to the infused norepinephrine is calculated by adding the five systolic and the five diastolic pressure readings, respectively, by dividing both sums by five and by subtracting the average of the last three basal blood pressure readings from the infusion pressure averages. (For instance, if the average basal blood pressure was 100/60 and the infusion pressures were 116/70, 128/82, 140/90, 138/90, 144/94, the average of the latter is 133/85, and the recorded rise above the basal pressure is +33/+25 mm. Hg).

It happens occasionally that the drops in the Venopak unit do not fall as fast as the metronome indicates. Unless the cannula has been dislocated and the fluid enters subcutaneous tissue, the trouble is usually that the small amount of cotton in the aluminum cap on the outside of the Venopak unit is impassable to air. The aluminum cap can be pulled

*Winthrop Laboratories. New York, N. Y.

off and discarded; if this does not help, a small metal ball valve inside the small black tube from which the aluminum cap was removed may have become immobilized and thus may obstruct the entry of air. This can be remedied by poking the ball upward with a sterile cannula.

In case the test has not been running smoothly, the procedure may be repeated after the original basal blood pressure level has been re-established.

Summary

Exaggerated pressor responses to intravenously infused l-norepinephrine (0.3 mcg. per kilogram per minute during 5 minutes), occurring after the thirtieth week of gestation, are probably due to abnormally increased mineralocorticoid activity. An average rise of the systolic blood pressure amounting to 50 mm. Hg or more is strongly suggestive of impending toxemia. Even in otherwise completely asymptomatic patients, it makes the immediate institution of drastic prophylactic measures, especially rigid sodium restriction, mandatory.

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TOXEMIA OF PREGNANCY: A NEW TREATMENT FOR CONTROLLING EDEMA*

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IN TITLING this paper we hasten to cite Strauss'[23] admonition of eighteen years ago: "The term 'toxemia of pregnancy' has served for generations and still serves as a diagnostic wastebasket to cloak ignorance."

Prevention of Edema

It has been known since time immemorial, however, that the development of edema during pregnancy is an ominous sign,[13] and although it does not always precede the development of true eclampsia, we consider abnormal weight gain a toxic sign and attempt to arrest it. We agree with Thornton[28] that ". . . good prenatal care will not prevent all toxemias of pregnancy, but adequate care will enable a physician to detect it in its incipiency."

Celsus (25 B.C.-A.D. 50) recognized the significance of edema in pregnancy and recommended that urinary output equal or exceed fluid intake. Zangemeister[30] was the first to attach significance to abnormal gain in weight and blamed it on the retention of water.

There is overwhelming evidence that there is altered hormone activity during pregnancy,[1, 13, 19] and Taylor and associates[24] demonstrated that estrogens are a contributing factor in retention of sodium, which predisposes to edema. There is also evidence that an antidiuretic substance is at work during clinical edema and that the regulation of sodium excretion is under the influence of the adrenal cortex.[21, 26] Dieckmann[13] held for years that pre-eclampsia and eclampsia are due to an abnormal water and electrolyte balance, and Strauss[23] has pointed out that "many methods of treatment which have met with more or less success have knowingly or unknowingly been measures to eliminate water retention."

Search for Better Therapy

Arnold and associates[4] popularized water restriction, and Strauss[23] and others have long recommended sodium restriction.[11, 12, 13] Such restrictions pose a hardship for the patient, however, and may actually prove dangerous. Dieckmann[13] advised that "the low sodium diet should be restricted to those patients who may benefit from it, and it should not be used longer than three weeks." Hormone therapy has been tried and found wanting and, of all the usual diuretics which may be effective in treating edema, only ammonium chloride or magnesium sulfate seems to be of much value in the edema of pregnancy and then only in conjunction with a low-sodium, high-protein diet. Thus, a more satisfactory method of treatment has been sought.

*Presented at the Medical Symposium, Eightieth Anniversary, Meharry Medical College, June 5, 1956.

Premenstrual Edema—Edema of Pregnancy

It was the recent widespread interest in, and treatment of, premenstrual tension with a new compound that prompted us to try the preparation in the edema of pregnancy. Green and Dalton[9, 15] commented, "The Study of both diseases revealed a striking similarity of symptoms and signs suggesting a common etiology." Heilig[18] noted the disturbed water metabolism during the menstrual cycle, and Petersen and Milles[20] described the altered capillary permeability which occurs during the premenstrual week. Thomas[26] compared the sudden diuresis which occurs after the menstrual flow with the diuresis which accompanies parturition. Pregnanediol may in some way be involved, since its secretion occurs after ovulation and stops 1 to 4 days before the flow, but its presence persists in the urine if pregnancy occurs.[17, 29] Pregnanediol secretion reaches its peak several weeks before parturition, and disappears 24 to 28 hours after delivery.[17] Smith[22] stated, "A decreased excretion of estrogen and pregnanediol has in every case so studied been found to precede any clinical manifestation of preeclampsia and eclampsia."

A New "Anti-Edema" Preparation

With these factors in mind it seemed logical to us that a drug which is more satisfactory than older forms of therapy in preventing the edema and other symptoms during the premenstrual week should be equally superior in treating edema of pregnancy. The preparation is a combination of a new 8-bromotheophyllinate compound and pyrilamine maleate,* and its use was first reported by Bickers.[7, 8]

Of special significance to us was the fact that in addition to Bickers' report of the clinical effectiveness of neo Bromth, he[8] also demonstrated that the preparation would effectively block the known antidiuretic effect of experimentally injected Pitressin, whereas ammonium chloride failed to do so. Greenblatt[6] later confirmed the diuretic properties of neo Bromth experimentally and commented on its superiority to ammonium chloride in removing sodium, potassium, and chloride ions as well as water. Another important finding was that "the greatest increase [in water recovery] is seen during the week when the animals received one per cent NaCl in their drinking water." Greenblatt[16] also stated that, clinically, he shares "Bickers' enthusiasm for this drug."

Evaluation in 180 Pregnant Patients

During the past 2 years we have evaluated neo Bromth in a total of 180 pregnant women, all of whom presented the classic signs of developing edema when first treated. The investigation was carried out in the antepartum clinics of the George W. Hubbard Hospital of Meharry Medical College. In each case, weight gain continued to increase above desirable limits, with an increase in blood presure, albuminuria, and pitting edema present in most. Beck[5] recommends that "fluid retention should be suspected whenever the gain in weight exceeds on pound per week in the latter months." However, we agree with Dieckmann[13] who stated, "It appears to be the rate at which gains in weight occur instead of the total amount of weight gain which is of first importance." He notes that some patients may gain as much as 15 kilograms or more without developing pre-eclampsia or eclampsia, while others develop severe toxemia on a much smaller total gain.

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*Supplied, as neo Bromth Tablets, through the courtesy of the Brayton Pharmaceutical Company, Chattanooga 9, Tenn. Each tablet contains 50 mg. 2-amino-2 methyl-1-propenol 8 bromotheophylinate and 30 mg. pyrilamine maleate.

We did not attempt to alter our patients' dietary habits or restrict fluid intake. Strauss[23] commented as early as 1939 that an *increase* in water intake can eventually lead to dehydration, other things remaining equal. Today, many clinicians advise an increased fluid intake; de Alvarez[11] advocates flooding the patient with water (up to 4,000 c.c. daily) to promote diuresis in edematous pregnant patients.

Results

Initial results were not particularly encouraging because of the fact—as we later learned—that to be effective in treating edema of pregnancy the preparation must be given in more than twice the dosage which Bickers, Greenblatt, and others employed in treating premenstrual tension. A few patients did respond on 2 or 3 tablets twice a day, but the majority required larger doses; a few were given a dozen or more tablets daily to bring their weight down and correct the edema. In most cases, 8 to 10 tablets daily were effective.

We found neo Bromth to be as superior to other therapeutic measures in our edematous pregnant patients as Bickers and Greenblatt found it to be in treating premenstrual tension. Of the 180 patients treated with neo Bromth, 162 (90 per cent) responded satisfactorily. Weight gain was arrested, elevated blood pressure, where present, was reduced, and edema and albuminuria were reduced or eliminated.

Only 18 (10 per cent) of the patients in this series failed to respond. In each case, weight gain continued to increase above desirable limits, with increased blood pressure and albuminuria present in most, despite administration of neo Bromth, ammonium chloride, or magnesium sulfate. We found it necessary to adopt the more rigorous regimen of low-salt diet, increased fluid intake, and bed rest with these patients. We also continued administration of neo Bromth, ammonium chloride, or magnesium sulfate, but urinary studies were inconclusive. neo Bromth did increase urinary output volume somewhat, but none of these agents had any appreciable effect in arresting weight gain, or reducing blood pressure or albuminuria. One patient went into severe eclampsia but recovered as expected after delivery of a stillborn infant. The medication itself appeared to be nontoxic. No side reactions attributable to the preparation occurred. A few patients complained of the annoying discomfort (nausea, vomiting, etc.) typical of normal pregnancies, but these occurred indiscriminately before, during, and after therapy.

TABLE I. SUMMARY OF STATISTICAL DATA IN 180 PREGNANT PATIENTS

AGE (YEARS)	NUMBER OF CASES	AVERAGE WEIGHT CHANGE (POUNDS)	AVERAGE BLOOD PRESSURE (MM. Hg)
162 Successes.—			
13-20	45	1.2 (increase)	4.9 (decrease)
21-35	88	0.3 (increase)	9.34 (decrease)
Over 35	29	1.8 (decrease)	10.8 (decrease)
18 Failures.—			
13-20	4	8.0 (increase)	21.0 (increase)
21-35	5	1.4 (decrease)	8.0 (decrease)
Over 35	9	2.4 (increase)	2.3 (increase)

Some of our patients had previously been on ammonium chloride, but since we could free them from a low-sodium, high-protein diet with neo Bromth, we switched medication to the new preparation in each case.

As Bickers suggests, neo Bromth seems to work specifically against an antidiuretic hormone and, as Green and Dalton[9, 15] reported, the latter agent is apparently responsible for producing edema in some women both during the premenstrual week and during pregnancy. Dalton[9] cites striking statistics to the effect that of 237 women who developed toxemia during pregnancy, 86 per cent complained of premenstrual tension during the menstrual cycles following childbirth.

Summary

1. Since excessive water retention does not always produce visible outward symptoms, we agree with the almost universally held view that weight gain is the safest and most reliable way in which to detect the early stages of edema.

2. The similarity between premenstrual edema and edema of pregnancy is discussed, and the literature is cited which suggests that an antidiuretic hormone plays the etiological role in both conditions.

3. A new preparation, neo Bromth, combining an 8-bromotheophyllinate compound with pyrilamine maleate, was investigated in 180 pregnant patients, to control existing or developing edema. All but 18 (10 per cent) responded satisfactorily. Weight gain was arrested, blood pressure was reduced, and edema and albuminuria were reduced or eliminated.* None of the 162 patients (90 per cent) who responded to the new medication developed any drug-induced side effects. Before, during, and after neo Bromth therapy, a few patients complained of the usual mild discomforts (nausea, etc.) which are characteristic of pregnancy.

4. None of the 18 patients who failed to improve responded to any other measures; all exhibited various degrees of toxemia. All required bed rest, with low-salt, high-protein diets. One developed full-blown eclampsia but recovered following delivery of a stillborn infant.

5. The drug, although nonhormonal therapy, appears to possess a specific antidiuretic hormone antagonism, which would account for its effectivenes in both premenstrual tension and edema of pregnancy.

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HYDATIDIFORM MOLE AND TOXEMIA OF PREGNANCY

With Unusual Late Development of Lutein Cyst

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THE recent publication of a case of hydatid mole complicated by toxemia of pregnancy and the unusual behavior of the complicating lutein cyst in a patient recently seen by me prompts the reporting of this case.

Mrs. F. P. was a 29-year-old woman with a history of one previous full-term pregnancy. Her last menstrual period had begun on October 29 and I saw her in consultation on February 27. For five weeks she had had nausea and vomiting of moderate severity and during this time had had constant vaginal bleeding, varying from spotting to the saturation of a small pad daily. On examination the uterus was larger than the calculated date of pregnancy would warrant. The tentative diagnosis was severe anemia, toxemia of pregnancy, and the possibility of hydatidiform mole. On admission her temperature was 98.3° F., pulse 116, blood pressure 160/100, red blood count 2.6 million, with a hemoglobin of 63 per cent. The blood smear suggested "anemia of a pernicious type probably on a toxemia basis." Urinalysis showed 4 plus albuminuria with fine and coarse granular casts.

During the next two days the patient rapidly became worse, jaundice appeared and she complained of headache. The icteric index was 30 and the nonprotein nitrogen 35. Permission was sought to empty the uterus because of the conviction that this was a case of hydatid mole. The family, still thinking that the patient was pregnant and because of religious belief, refused this permission until March 3 when her condition had become critical. She was dull and apathetic and markedly dyspneic with a thready pulse ranging between 140 and 160.

She was taken to the delivery room, the membranes were ruptured, and the soft and partially dilated cervix and vagina were tightly packed with gauze. It did not seem at the time as though the patient's condition would permit of any more radical method of emptying the uterus. Within thirty minutes she had bled through the pack, which was removed and a No. 4 Voorhees hydrostatic bag introduced through the cervix and inflated. All hemorrhage ceased, contractions started, and a second transfusion was given. At 3:40 P.M. March 4 the bag and a hydatid mass the size of a large grapefruit were expelled. The uterus was curetted and packed.

Microscopic examination of the tissue showed the chorionic villi with cystic degeneration. A large part of the decidual tissue and many chorionic villi were necrotic, but there was no evidence of malignancy. The diagnosis was hydatid mole.

The improvement in the patient's condition was dramatic and immediate. Within twelve hours she was retaining fluids by mouth and was alert and said she felt very much better. She received two more transfusions. This improvement continued and on March 11 the red blood count was 3.3 million and the hemoglobin 70 per cent. She was discharged on March 13.

On April 7, or about five weeks following the expulsion of the mole, she reported to the office, looking much better than when she left the hospital but complaining of lower

abdominal discomfort and a slight bloody spotting. An abdominal and vaginal examination disclosed a soft movable mass in front of the uterus, the size of a 3 months' pregnancy. The cervix was soft and patulous and there was a mucosanguineous discharge. A Zondek-Friedman test was done with three rabbits. The first, which received 10 c.c. of urine, showed a moderately positive reaction. However, both the second rabbit injected with 4 c.c. and the third which received 1 c.c. were negative. The diagnosis was lutein ovarian cyst of rapid growth with no evidence of chorionepithelioma.

On April 8 a curettage and a conservative oophorectomy were done, with some ovarian tissue left on the affected side. The pathological examination showed a multilocular cyst 14 cm. in diameter filled with yellow, slightly blood-tinged fluid. The uterine curettings showed decidua of pregnancy, inflamed uterine mucosa, but no chorionic villi were seen and no evidence of malignancy. On May 24 four rabbits were injected with 1, 4, 10, and 20 c.c. of urine. The first two were negative and the third and fourth were not examined, indicating that at this time chorionepithelioma could be ruled out with safety. One year later a Zondek-Friedman test was negative. She has never conceived again, however, and a few years after the oophorectomy she underwent a hysterectomy for fibroids.

Comment

Crowell[2] reported toxemia in 4 cases out of 15 of hydatidiform mole, or 26.7 per cent. In 3 the toxemia was severe. Chesley, Cosgrove, and Preece[3] collected 35 cases and added one of their own of probable or alleged eclampsia associated with hydatidiform mole, with 5 deaths, or a 14 per cent mortality rate. Dieckmann[5] found toxemia in 3 of 30 cases of hydatid mole, while Page[4] reported toxemia in 10 out of 30 moles. In a very large series of 85 cases of hydatid mole, Acosta-Sison[7] of the clinic of the University of the Philippines cited 31 cases with symptoms of toxemia. Mueller and Lapp's[6] case was unusual in that the eclampsia occurred one week after the mole was passed. Chorionepithelioma followed in this case and the patient was alive and well two years after complete hysterectomy.

Several observers noted that the toxemia was severe only in the cases where the uterus had reached the height of the umbilicus or beyond, or after amenorrhea of from 4 to 7 months.

The tendency toward the development of lutein ovarian cysts following hydatid mole has been noted before, but most observers have said that these regressed after the removal of the mole. In the case here reported, however, the cyst increased rapidly in size after the uterus was emptied with the chorionic gonadotrophic hormone falling.

Two interesting facts emerge from this review of the literature: First, hydatidiform mole occurs more frequently than has been estimated in the past. The Margaret Hague group, Chesley, Cosgrove, and Preece, reported 1 case in 1,321 pregnancies, Mueller and Lapp from Kings County in Brooklyn a similar proportion of 1 in 1,349. Crowell gave an incidence of 1 in 759 deliveries and from the Philippines one clinic reported 85 cases of hydatidiform mole with no note of the total number of obstetrical cases, which must have been enormous. The second fact is that toxemia not only is a common accompaniment of mole but it may be fatal.

Summary

1. A case of hydatidiform mole is reported with toxemia so severe as to threaten life.

2. The case was characterized by the unusual development of a large lutein cyst, rather than its regression, after passage of the mole.

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LUPUS ERYTHEMATOSUS SIMULATING TOXEMIA OF PREGNANCY

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ALTHOUGH disseminated lupus erythematosus is a relatively uncommon disease, it has a predilection for young women during the childbearing age, and the association of lupus with pregnancy should not be overlooked. There are many reports of this association to be found in the literature.[1-4]

The following case is one in which pregnancy was complicated by lupus erythematosus although, at the time of the pregnancy, the patient gave none of the usual manifestations of lupus. The diagnosis was not made until some time later. In this case the signs of abnormal renal function were most prominent and resulted in the diagnosis of chronic nephrosis with superimposed toxemia of pregnancy.

Case Report

Mrs. M. R., a 23-year-old white para i, gravida ii, was admitted on Nov. 1, 1955, for treatment of excessive weight gain, albuminuria, moderately severe edema, and urinary tract infection associated with a pregnancy of 35 weeks' gestation. She had had dependent edema since early in her pregnancy with recent rapid weight gain (7 pounds in the previous week) which failed to respond to Diamox. She had gained 35 pounds since the onset of her pregnancy and had right flank pain and dysuria of one week's duration.

The patient was somewhat pale and lethargic, and there was pitting edema of both legs, with moderate edema of the hands, face, and trunk. The blood pressure was 130/88.

The past history disclosed that the patient had had a mild throat infection in 1951 and a pleural effusion with moderately high fever in 1953, the etiology of which had not been determined. Since 1953 she had been somewhat anemic. In April, 1954, during the patient's first pregnancy, labor was induced because of moderately severe edema of the legs, arms, and face and pronounced albuminuria. No record of the blood pressure was available. Six weeks later she developed thrombophlebitis of the right femoral vein, and was hospitalized at Milwaukee Hospital for the first time. The blood pressure on this admission was 118/60. Urinalysis showed evidence of kidney damage (Table I).

The patient was given Dicumarol, Achromycin, and 500 c.c. of whole blood. There was gradual improvement of the phlebitis, and the urinary tract infection cleared rapidly. However, daily urinalysis continued to show 30 to 150 mg. per cent of albumin with occasional erythrocytes and hyaline casts. On May 29, 1954, she was discharged with the additional diagnosis of subacute glomerulonephritis.

On June 6, 1955, the patient was admitted following a sudden episode of syncope which occurred without prodromas, and with pain in the right leg of one week's duration. The only positive physical findings were moderate edema and tenderness in the right calf

region. The blood pressure was 98/60. The last normal menstrual period was March 7, 1955; pelvic examination confirmed pregnancy of three months' duration. Hypochromic anemia was present, but there were no abnormal urinary findings (Table I).

Dicumarol, iron, and prophylactic Gantrisin were given, and the patient was discharged improved nine days later.

During the first three months following her discharge from the hospital, the patient's prenatal course was not remarkable. In September, 1955, she was given Diamox for slight ankle edema and excessive weight gain. The blood pressure was 110/70 and there was no albuminuria. However, on Oct. 3, 1955, albuminuria was noted for the first time. The albuminuria persisted and increased and was associated with gradual elevation of the blood pressure and progressive weight gain until the present admission (Table I).

A diagnosis of toxemia of pregnancy with pyelonephritis superimposed on chronic nephrosis was made, and Diamox, Achromycin, and 500 c.c. of whole blood were given. However, the patient's condition showed no improvement, and on November 4 it was noted that the blood pressure was 140/90 and that there had been some increase in anasarca. In view of these findings and a progressive increase in the albuminuria, it was felt that the pregnancy should be terminated. On Nov. 5, 1955, following medical induction and an uneventful labor, the patient was delivered of a 4 pound, 8 ounce female infant who did very well after birth. At the time of delivery the patient's blood pressure rose to 160/104, but shortly thereafter it fell to 140/90 and in twelve hours was 120/70. Within twelve hours of the delivery diuresis occurred, with an output of 3,900 c.c. and 4,260 c.c. on the first two days.

During the remaining period of hospitalization the patient showed steady improvement although the urine continued to contain 50 to 200 mg. per cent of albumin. She was discharged on Nov. 13, 1955.

Subsequent Admission.—On Feb. 22, 1956, the patient was readmitted because of chills, fever, malaise, joint pains, weakness, and edema which had their onset one week prior to admission following a mild upper respiratory tract infection. This was the first time that she had complained of any joint pain.

She was not only acutely, but chronically ill. There were marked pallor and evidence of poor nutrition. No evidence of icterus or acute inflammation of the joints was noted. The spleen was not palpable. The blood pressure was 140/80 and the temperature 101.8° F. Marked anemia and evidence of kidney damage were present (Table I).

Because of the fever and clinical evidence of systemic infection, penicillin was given. When urine cultures revealed *E. coli* highly sensitive to erythromycin, this drug was given too. Due to the profound anemia, the patient received 3,000 c.c. of whole blood which raised the hemoglobin to 10.8 Gm. per 100 c.c. on February 27.

The patient showed gradual clinical improvement, and on March 2 she was afebrile and had no complaints. She received general supportive therapy plus a high-protein diet, vitamins, and minerals. In spite of the apparent clinical improvement, however, the hemoglobin had fallen to 6.9 Gm. per 100 c.c. on March 6. There was no hematuria, melena, or other evidence of blood loss. X-rays of the chest and the entire gastrointestinal tract were negative. On March 7 the serum bilirubin was 1.42 mg. without clinical evidence of jaundice. There was no bilirubin or urobilinogen in the urine, and osmotic cell fragility and platelet counts were normal. Since the patient had a positive indirect Coombs' test, 4.6 per cent circulating nucleated erythrocytes and 7.3 per cent reticulocytes, in addition to the slight elevation of the bilirubin, it was felt that she had acquired hemolytic anemia. Lupus erythematosus was considered, and on March 9, L. E. cells were found in peripheral blood L. E. preparations. The patient was given an additional 2,000 c.c. of whole blood which raised the hemoglobin to 9.0 Gm. per 100 c.c. On March 12 steroid therapy was initiated with corticotropin gel, and this was then changed to prednisolone. In ten days the hemoglobin rose to 11.0 Gm., and the reticulocyte count fell to 1.1 per cent and the bilirubin to 0.60 mg. The patient's appetite improved, and she gained weight without evidence of edema. Symptomatically she also felt improved, and on March 24 she was discharged from the hospital.

TABLE I. LABORATORY DATA

	6/15/54 6 WEEKS POST PARTUM	6/6/55 13 WEEKS' GESTATION	11/1/55 34 WEEKS' GESTATION	11/7/55 2 DAYS POST PARTUM	2/22/56 16 WEEKS POST PARTUM	2/27/56	3/6/56	3/22/56 (10 DAYS OF ACTH AND CORTISONE THERAPY)	5/4/56
Blood pressure	118/60	98/60	140/90 to 160/104 in labor	120/70	140/80				
Blood transfusion				500 c.c. at delivery		3,000 c.c.			
Blood:									
Hemoglobin (Gm. %)	10.0	9.6	10.3	9.6	4.6	10.8	6.9	11.0	12.8
Erythrocytes (millions)	3.7		3.16		1.71				
Hematocrit		34		29					42
Leukocytes			8,600		11,600				
Nonprotein nitrogen (mg. %)		32	34	33	57				
Uric acid (mg. %)			5.4						
Total protein (Gm./100 c.c.)			3.27	3.55		4.92			
Albumin (Gm./100 c.c.)			1.75	2.15		1.90			
Globulin (Gm./100 c.c.)			1.52	1.38		3.02			
Sodium (meq./L.)			141.6						
Potassium (meq./L.)			4.08						
Chlorides (meq./L.)			113.8						
Carbon dioxide (meq./L.)			12.3	17.7					
Urine:									
Specific gravity	1.030	1.010	1.020	1.013					
Albumin (mg. %)	100	0	500-2,000	150	2,200				0
Microscopic:									
Erythrocytes per high-power field	Occasional	Occasional	4-8	15-20	0				0
Leukocytes per high-power field	Clumps	Occasional	Many	Few	2-3				0
Casts per low-power field	Many hyaline granules		Many	Many	Many				0
Culture					*E. coli*				

Since her discharge from the hospital her progress has been very satisfactory. On May 4, 1956, the hemoglobin was 12.8 Gm. and the hematocrit 42; there were no L. E. cells noted on peripheral blood L. E. preparations. At the present time, nine months since the patient's hospitalization, she is asymptomatic and has no evidence of acute or chronic disease. There is no evidence of renal insufficiency. She is being maintained on 10 mg. crystalline prednisone daily plus 80 units of corticotropin gel every four weeks. She is on a low-salt diet and receives small amounts of added potassium chloride.

Comment

Lupus erythematosus disseminatus is a disease of multiple systemic involvement[6] which results in many and varied manifestations such as edema, skin lesions, arthralgias, hypochromic anemia, and evidence of renal insufficiency. All of these signs and symptoms, however, may also be found in pregnancy and, when they occur for the first time in the pregnant patient, the diagnosis of lupus may be obscured. Nearly all of the cases reported in the literature are those in which pregnancy occurred subsequent to the diagnosis of lupus. Our case is unusual in that the diagnosis of lupus erythematosus was not established until some time after the patient's second pregnancy although in retrospect it seems probable that the patient had lupus in 1953 when she was hospitalized with a pleural effusion.

Although lupus erythematosus is a rare complication of pregnancy, the inclusion of lupus in the differential diagnosis of all but the most typical cases of toxemia may be lifesaving, and a meticulous search for L. E. cells in peripheral blood preparations should be made. Untreated lupus during pregnancy often carries a grave prognosis for both the mother and the fetus, and the outcome of this case was most fortunate.[1, 2, 4, 5] There is increasing evidence that if the diagnosis of lupus is made, well-controlled administration of corticosteroids should aid considerably in reducing the high mortality rates.[2, 7]

With the advent of steroid therapy in lupus erythematosus, the lives of many young women with lupus have been prolonged. Since these drugs generally do not inhibit ovulation or interfere with pregnancy, obstetricians will be called upon to treat more patients with lupus in the future, and they should be aware of the problems which may arise in these cases.

Summary

A case of lupus erythematosus during pregnancy, erroneously diagnosed, is presented with the suggestion that the signs and symptoms of abnormal renal function during pregnancy may indicate the presence of lupus rather than nephrosis, nephritis, or toxemia of pregnancy.

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REDUCTION OF THE PERINATAL MORTALITY OF CESAREAN SECTION

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IN THE course of an effort to define the area of obstetrical responsibility for the mortality of the first day of life, the Brooklyn Committee on Maternal Welfare found that 27 per cent of these deaths occurred in the course of operative delivery. Cesarean section was associated with 38 per cent of this mortality.[1]

At present the comparative safety of cesarean section invites critical examination of the operative procedure and its relation to the life of the fetus. From the number of fetal deaths (stillbirths) associated with operation, and the infant deaths of the early postoperative period, the perinatal mortality rate may be readily calculated. This rate should be a vital part of the measure of worth of the operation, because the fetal mortality associated with cesarean section does not fail of report, and infant death usually occurs early in the puerperium.

To be tabulated as fetal death in the course of cesarean section the fetus "must not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles"[2] before its extraction from the uterus is complete. Even competent observers may not be in agreement. This is a good reason why the fetal mortality and the neonatal mortality associated with cesarean section should not be separated. However, in order to discover so far as possible *why* death occurred, perinatal deaths must be listed as fetal or neonatal, and in weight intervals of 500 grams according to the indication for operation.

Material for Study

Certificates of fetal death with matching certificates for birth and neonatal death associated with all the cesarean sections performed in Brooklyn during 1955 were furnished by the Bureau of Records and Statistics of the Department of Health of the City of New York. In many cases additional information was obtained from hospitals.

In 1955, 37 Brooklyn hospitals reported 2,804 births by cesarean section; 2,743 infants were born alive, and there were 61 fetal deaths. The official figures are shown in Table I.

Since statisticians commonly report the number of cesarean sections by births, not by actual number of operations, 3 infants of twin deliveries must be deducted from this total. Three operations associated with fetal deaths are likewise excluded as not cesarean section, since the fetus was found free

in the peritoneal cavity. Available for this study, then, are 2,798 cesarean sections associated with 97 neonatal deaths and 58 fetal deaths. The perinatal mortality rate was 55 per thousand. No correction has been made for congenital anomalies thought to be incompatible with life (5 cases). Cesarean section rates should not be corrected.

TABLE I. OFFICIAL BIRTH STATISTICS RELATED TO CESAREAN SECTION, BROOKLYN, 1955

All Births.—	
Total live births	56,680
Total fetal deaths	6,636
Fetal deaths (28 weeks and over)	760
Maternal deaths	34
Births by Cesarean Section.—	
Live births	2,743
Fetal deaths	61
Infant deaths (less than 7 days)	71
Perinatal mortality rate*	52

* $\frac{97 \text{ plus } 61}{2743 \text{ plus } 61} \times 1{,}000.$

The fetal death certificate provides for the cause of death as determined (a) in the fetus, (b) in the mother, and (c) contributory causes in either fetus or mother. It has been well said that "such a breakdown may appear logical but it might be questioned whether more might not be gained by emphasizing the relationships between mother and fetus rather than their separation."[3] As a matter of fact this is accomplished, though very inadequately, in official tabulation which assigns fetal death to maternal causes except in the case of congenital malformations, birth injury, and some conditions of the umbilical cord. Except in a few instances, the diagnosis of the pathologist did not clearly point to any controllable factor of death. In the 58 cases of fetal death studied, though 19 autopsies were reported, death was largely attributed to maternal causes.

In the certificates of neonatal death, sequence of events was largely disregarded by the physician. Our lack of knowledge of the basic causes of neonatal death, as well as of fetal death, is probably the reason for this. Autopsy was performed in 57 cases of neonatal death.

Since parity and age of the mother are generally held to be important factors in perinatal mortality, these data are shown in Table II.

TABLE II. PERINATAL MORTALITY OF CESAREAN SECTION IN RELATION TO AGE AND PARITY OF MOTHER

	NUMBER OF LIVE BIRTHS PREVIOUSLY							
AGE IN YEARS	0	1	2	3	4	5 AND MORE	UNKNOWN	TOTAL
15-19	3	2						5
20-24	12	8	2	1		1		24
25-29	11	16	5	5	4	1		42
30-34	12	12	8	7		5	2	46
35-39	5	6	6	5	1	2	1	26
40-44	4	1			2	4		11
45 and over				1				1
Totals	47	45	21	19	7	13	3	155

Some deductions based upon the indication for cesarean section should be valid. The fetal and infant deaths associated with the indications for operation are set down in Table III.

TABLE III. INDICATION FOR CESAREAN SECTION, BROOKLYN, 1955

INDICATION FOR OPERATION	PERINATAL DEATHS	
	FETAL	INFANT
Abruptio placentae	29	12
Placenta previa	9	22
Previous cesarean section	7	34
Dystocia	9	13
Toxemia	1	10
Miscellaneous	3	6
Total	58	97

Correlation of Mortality and Indication for Operation

The important obstetrical indications for cesarean section associated with perinatal death were dystocia, toxemia, previous cesarean section, and antepartum hemorrhage. The number of deaths in each one of these categories closely approximated our experience of the previous year. Deaths were studied in order to discover, if possible, the controllable factors, and case reports were presented at open conferences on obstetrical mortality with the idea of stimulating wide discussion of current cesarean section practice and technique with special reference to the safety of the fetus. Criticism was not confused with faultfinding.

That 14 per cent of the perinatal deaths were associated with dystocia is notable. Breech and shoulder presentations, long labor, trial forceps, inertia, failed version, and disproportion were mentioned on the death certificates. For the most part, however, death could hardly be attributed to dystocia even though resulting from it. Often the fetus was subjected to operative trauma and anesthesia before cesarean section was performed.

Toxemia was usually reported as severe. In every case but one, operation was performed at 31 weeks or later; only one infant weighed more than 2,500 grams. In only one case was the fetus born dead.

Antepartum hemorrhage preceded perinatal death in 72, or 46 per cent, of the cases. In abruptio placentae 70 per cent of this mortality was fetal; in placenta previa 70 per cent of the death rate was neonatal.

TABLE IV. PERINATAL MORTALITY OF CESAREAN SECTION. BIRTH WEIGHT IN MAJOR INDICATIONS

WEIGHT IN GRAMS	PLACENTA PREVIA		ABRUPTIO PLACENTAE		PREVIOUS CESAREAN	
	FETAL	INFANT	FETAL	INFANT	FETAL	INFANT
Less than 1,000		2	1	2		2
1,001-1,500		6	2	2	1	5
1,501-2,000		3	6	6	2	2
2,001-2,500		5	2			8
2,501-3,000	2	2	4			9
3,001-3,500		1	2	1		4
3,501-4,000						3
4,001-4,500	2					
4,501-5,000	2				1	
Over 5,000						1
Unknown	3*	3	12†	1	3	
Total	9	22	29	12	7	34

*All 32 weeks and over.
†Nine were 36 weeks and over.

The mother had undergone previous cesarean section in 41 cases of perinatal death, or 26 per cent of the total. In 7 cases the fetus was born dead; in 2 of these placental separation compelled operation, in 2 others the fetus

was known to be dead of erythroblastosis, and in 3 cases fetal death was unexpected. Prematurity was an impressive factor, as more than half of the operations were performed before the thirty-sixth week, 3 as early as 26, 27, and 28 weeks, because of the onset of labor or early rupture of the membranes.

Previous cesarean section and antepartum hemorrhage were together associated with 73 per cent of all the perinatal mortality of cesarean section. In the fetal death group weights were not well reported. Only 30 per cent of the infants born alive weighed more than 2,500 grams each. The incidence of premature delivery in these major groupings is seen in Table IV.

Comment

The prime object of this investigation was to find the controllable factors in the perinatal mortality of cesarean section. The importance of prematurity is obvious. Comment is made only after reference to all the facts discovered.

Perinatal death due to dystocia is largely controllable. Seldom is operation indicated when the fetus is dead. Birth trauma associated with protracted labor, trial forceps, and scapular presentation may be avoided. The role of anesthesia is far subtler, less tangible, and probably more important in prematurity. However, no deductions as to the risk of anesthesia can be made from this study.

When cesarean section is performed because the patient has been previously delivered abdominally, prematurity is often added to the hazards of the fetus. Obviously the optimum time for operation is as close to term as possible, certainly later than 38 weeks.

A roentgenogram for demonstration of the lower femoral epiphyses of the fetus may be helpful.[4] In any case Dieckmann's[5] antepartum dehydration plan may reduce infant mortality. Some who have become expert in assessing the degree of ripeness of the antepartum cervix find this a good criterion of fetal maturity. In spite of the practical objections that attend awaiting the onset of labor, it is probably best to do so. If the membranes rupture or labor begins prematurely, before the thirty-eighth week, pelvic delivery should be given serious consideration.

There were 5 perinatal deaths due to erythroblastosis. Isoimmunization is not a good reason for cesarean section. The premature baby with hemolytic disease does badly, and is prone to kernicterus. Death in utero is better than that. If cesarean section is not performed in the first place, the risks and anguish of one fruitless cesarean section after another will be avoided. Early termination of pregnancy may be justified, but not by cesarean section.

In abruptio placentae cesarean section is often imperative even when the fetus is dead or nearly so. Even slight placental separation may be attended by high fetal mortality. If labor should not progress smoothly and rapidly after rupture of the membranes and uterine stimulation, earlier cesarean section should reduce fetal mortality.

If the diagnosis should be placenta previa, the patient should not be examined rectally or vaginally other than by speculum inspection of the cervix. In the interest of the fetus the patient should remain in the hospital until the

thirty-sixth week or later when operation may be performed. MacAfee's[6] classic paper of a decade ago proved that expectant treatment is safe, but a great many remain unconvinced. Grant[7] has recently confirmed his findings.

The placenta of the premature fetus contains a greater proportion of the total blood volume than that of the baby at term. And the low-lying placenta is likely to cover a larger area and carry more blood than when normally implanted. Incision through the placenta, even pushing it aside, will cause severe fetal blood loss and increase perinatal mortality. Lower segment cesarean section should not be performed for placenta previa.

In any cesarean section, aside from that for placenta previa, details of technique may be important factors in lessening perinatal mortality. Often the operator's response to hemorrhage resulting from his incision into the uterus is automatic rapid extraction of the fetus and immediate clamping and cutting of the umbilical cord. In his anxiety to control maternal blood loss, he may hurry the baby out of the operative field. The fetus should be extracted slowly, and not until the first uterine contraction has taken place. The placenta is then removed manually and taken with the baby to a place where it may be suspended above the baby until all pulsation in the umbilical cord has ceased. This delay is of considerable importance. Windle[8] has shown that at least one fourth of the fetal blood volume at term is in the placenta and that prompt clamping of the cord is equivalent to birth hemorrhage. The blood in the placenta should be recovered; its loss may be a critical factor in perinatal mortality.

Summary

The perinatal mortality associated with performance of 2,798 cesarean sections in a large number of metropolitan hospitals during the same year is analyzed. That maternal complications increase the perinatal mortality rate is clear. Antepartum hemorrhage and previous cesarean section, largely because of prematurity associated with these operations, are the prime factors. Suggestions for lowering the perinatal mortality rate of cesarean section are presented.

The Brooklyn Committee on Maternal Welfare greatly appreciates the help of Carl L. Erhardt, Director of the Bureau of Records and Statistics, Department of Health, City of New York.

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32 Remsen Street

THE TRUE INCIDENCE OF SILENT RUPTURE OF CESAREAN SECTION SCARS*

A Prospective Analysis of 403 Cases

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SILENT rupture of a cesarean section scar is a common but a poorly documented entity. It was our impression that this occurs more frequently than has been reported in the literature.[1-4] A review of the records at our institution prior to 1953 did not confirm this impression because the status of the uterine scar at repeat cesarean section was rarely recorded unless symptomatic rupture had occurred. Because of the disparity between our clinical impression, the institutional records, and the findings in the literature, a prospective study was initiated in 1953 to ascertain the incidence of dehiscence of the uterine scar. In addition, an analysis was made of the factors that influence the healing of the scar, and its behavior in future pregnancies.

Definitions

In order to discuss this subject intelligently, we must define the terminology employed herein.

Rupture is considered to be complete when the edges of the scar are separated and the contents of the uterus present through the defect. This defect may involve a small section of the scar or all of it. In disruptions of the lower segment, the defect may not become evident until the overlying bladder and vesicouterine peritoneum are mobilized.

Rupture is considered to be incomplete when only the outermost edges of the myometrium are bridged by a thin, relatively avascular, translucent membrane of scar tissue.

A scar is considered to be intact regardless of its width or thickness if the edges of the myometrium are in complete apposition. It is not unusual to find a markedly and uniformly thin lower uterine segment at elective primary cesarean section (even in primigravidas). This observation per se at repeat cesarean section, therefore, does not indicate impaired integrity of the scar (Fig. 1).

Material

At the Jewish Hospital of Brooklyn from Jan. 1, 1953, through June 30, 1956, there have been 403 repeat cesarean sections. These patients had a total

*Presented at a meeting of the Brooklyn Gynecological Society, March 20, 1957.

of 482 previous cesarean section scars, of which 266 were transverse lower segment, 155 vertical lower segment, 33 classical; in 28 the type and location of the incision were unknown. Approximately one third of the patients had had cesarean section previously performed at other institutions; the data on these were obtained from the original hospitals. In the instances where complete information was unobtainable, the designation "unknown" was applied.

In this series there was a total of 48 disruptions of cesarean section scars, an incidence of 10.0 per cent; 40 were complete and 8 were incomplete. There were 22 transverse lower segment scars that ruptured, an incidence of 8.3 per cent; 20 vertical lower segment, an incidence of 12.9 per cent; and 6 classical, an incidence of 18.2 per cent. None of these presented classical symptoms or signs of rupture and all were incidental findings at time of operation. There were no maternal or fetal deaths due to rupture (Table I).

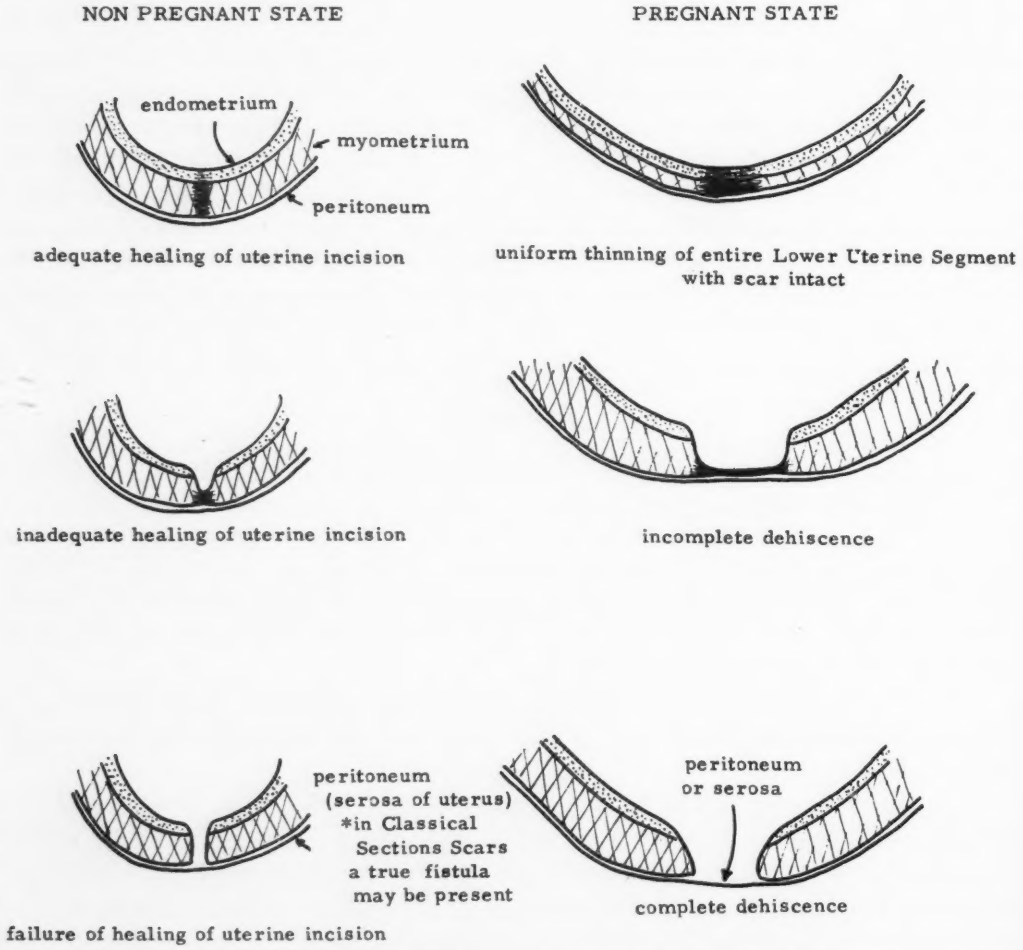
NON PREGNANT STATE
PREGNANT STATE
endometrium
myometrium
peritoneum
adequate healing of uterine incision
uniform thinning of entire Lower Uterine Segment with scar intact
inadequate healing of uterine incision
incomplete dehiscence
peritoneum (serosa of uterus) *in Classical Sections Scars a true fistula may be present
peritoneum or serosa
failure of healing of uterine incision
complete dehiscence

Fig. 1.—Healing and dehiscence of cesarean section scars.

Analysis of the Factors Concerned With Integrity of the Scar

Various criteria have been advanced as aids in ascertaining the integrity of the scar. Some appear empirical, and others, although commonly accepted, are not substantiated by the findings in this study. These factors are presented below.

TABLE I. DISRUPTION OF CESAREAN SECTION SCARS IN RELATION TO TYPE OF UTERINE INCISION

TYPE OF UTERINE INCISION	TOTAL SCARS	RUPTURE		TOTAL RUPTURE	INCIDENCE OF RUPTURE (%)
		COMPLETE	INCOMPLETE		
Transverse lower segment	266	19*	3	22	8.3
Vertical lower segment	155	16†	4	20	12.9
Classical	33	5†	1	6	18.2
Unknown	28	0	0	0	0.0
Grand total	482	40	8	48	10.0

*In 4 cases, the opening involved the entire length of the scar.
†In these cases, the lower angle was open in 9, the central portion of the scar in 4, the upper angle in 6, and the entire length of the scar in 2 cases.

Postoperative Course and Antibiotics.—Table II shows a slightly higher incidence of rupture in patients with morbid postoperative courses. This slight difference is not statistically significant. These data do show, however, that an afebrile postoperative course does not imply a good scar nor a morbid one a defective scar, and the degree and severity of the morbidity have little influence on the integrity of the scar.

TABLE II. INCIDENCE OF DEHISCENCE OF THE UTERINE SCAR IN SUBSEQUENT PREGNANCIES IN RELATION TO PREVIOUS POSTOPERATIVE COURSE

MORBIDITY	TOTAL SCARS	RUPTURED	
		NO.	%
Afebrile	272	23	8.5
One day	59	8	13.6
Two days	60	9	15.0
Three days	32	3	9.4
Four days	17	3	17.7
Five or more days	14	1	7.1
Unknown	28	1	3.5
Grand total	482	48	10.0

Incidence of Scar Rupture by the Morbidity Standards of the American College of Surgeons

Afebrile	9.4%
Febrile	13.0%

TABLE III. INCIDENCE OF DEHISCENCE OF THE UTERINE SCAR IN SUBSEQUENT PREGNANCIES IN RELATION TO PROPHYLACTIC ANTIBIOTIC THERAPY FOLLOWING PREVIOUS CESAREAN SECTION

MORBIDITY	ANTIBIOTIC THERAPY					
	NONE			GIVEN		
	NO. OF CASES	RUPTURES		NO. OF CASES	RUPTURES	
		NO.	%		NO.	%
Afebrile	73	4	5.5	199	19	9.5
One day	15	3	20.0	44	5	11.4
Two days	10	1	10.0	50	8	16.0
Three days	3	0	0.0	29	3	10.3
Four days	4	0	0.0	13	3	23.1
Five or more days	2	0	0.0	12	1	8.3
Grand total	107*	8	7.4	347*	39	11.2

*Data unavailable in 28 cases; one rupture occurred in this group.

The statement has been made that the prophylactic use of antibiotics will enhance good scar formation.[5, 6] As noted in Table III, prophylactic antibiotic therapy did not produce the anticipated effect on the incidence of rupture of the scar in subsequent pregnancies. A larger series must be studied to permit a more definitive statement on the value of antibiotics in relation to scar healing.

Interval Between Viable Pregnancies.—Are we justified in advising a specific time interval between cesarean section and subsequent conception? Does this interval influence the integrity of the scar? It is our feeling that good healing begins in the operating room and is usually completed within three months. This is borne out by animal experimentation[7, 8] and by the findings in this series. Table IV shows that the incidence of rupture is independent of the interval between cesarean section and subsequent viable pregnancy. The higher rate noted in the 6 to 11 month group is probably related to the indication for the previous section, namely, antepartum hemorrhage and fetal distress. Antepartum hemorrhage accounted for two thirds of the ruptures in this group, and 18.8 per cent of the total ruptures reported herein (see below).

TABLE IV. INCIDENCE OF DEHISCENCE OF THE CESAREAN SECTION SCAR IN RELATION TO THE INTERVAL BETWEEN VIABLE PREGNANCIES

INTERVAL	TOTAL SCARS	RUPTURED	
		NO.	%
0- 5 months	39	3	7.7
6-11 months	55	9	16.4
12-17 months	52	5	9.6
18-23 months	48	4	8.3
2- 4 years	194	18	9.3
4 or more years	94	9	9.6
Grand total	482	48	10.0

Uterine Distention.—Uterine distention, due to the enlarging products of conception, is thought to be a cause of dehiscence of cesarean section scars in subsequent pregnancies.[9] In most instances, however, the defect in the scar antedates the current pregnancy and is merely accentuated by it. This accounts for the general absence of symptoms associated with occult rupture.

One of the best indices with which to estimate the degree of uterine distention is the weight of the baby. Table V shows that rupture occurred with premature as well as term babies, and the incidence was approximately the same for all weight groups. Furthermore, excessive distention of the uterus due to polyhydramnios (8 instances), multiple pregnancies (3 instances) and large babies (4,000 or more grams) was not associated with scar separation.

TABLE V. INCIDENCE OF DISRUPTION OF UTERINE SCAR IN RELATION TO WEIGHT OF BABY DELIVERED BY REPEAT CESAREAN SECTION

WEIGHT OF BABY (GRAMS)	TOTAL SCARS	RUPTURED	
		NO.	%
1,000-1,999	12	1	8.3
2,000-2,499	27	4	14.8
2,500-2,999	153	15	9.8
3,000-3,499	195	21	10.8
3,500-3,999	75	7	9.3
4,000-4,499	16*	0	0.0
4,500-4,999	4†	0	0.0
Grand Total	482	48	10.0

*Includes two sets of twins.
†Includes one set of twins.

Labor.—In 71 cases of this series the repeat section was performed earlier than had been planned because of the onset of prodromal labor. In 15 of these cases, the edges of the scar were found to be separated. Although the incidence of rupture in this group is more than twice that of the group who had

elective operations (Table VI), the physical features of all the dehiscences were identical. There was no evidence of recent separation in any and they all appeared to be of long duration. What effect active labor would have on these or on the intact scars cannot be ascertained from this study, however, because of adherence to the dictum, "once a section always a section."

TABLE VI. INCIDENCE OF SCAR DEHISCENCE IN RELATION TO INDICATION FOR AND WEEK OF PERFORMANCE OF REPEAT CESAREAN SECTION

WEEK OF GESTATION	INDICATION FOR REPEAT SECTION						GRAND TOTAL	
	ELECTIVE		EARLY LABOR		ANTEPARTUM HEMORRHAGE			
	TOTAL	RUPTURED	TOTAL	RUPTURED	TOTAL	RUPTURED	CASES	RUPTURED
Less than 36	4	0	12	0	2	0	18	0
36	13	1	17	5	1	0	31	6
37	71	4	13	2	2	0	86	6
38	236	19	19	8	2	0	257	27
39	67	6	8	0	0	0	75	6
40	13	3	2	0	0	0	15	3
Grand total	404	33	71	15	7	0	482	48

Duration of Gestation in Subsequent Pregnancy.—The duration of subsequent pregnancy has little influence on the integrity of the scar (Table VI). The physical appearance of all of these ruptured scars indicated that an even earlier cesarean section would have shown identical findings.

Type of Uterine Incision.—In our study we have found that the most common uterine incision is the transverse lower segment, and the least common is the classical. This is a reflection of the custom of the community at large, and not only of our institution. Transverse scars, although least liable to rupture, accounted for 45.8 per cent of the total ruptures, and vertical lower segment scars for 41.7 per cent.

TABLE VII. INCIDENCE OF DISRUPTION OF CESAREAN SCAR IN RELATION TO THE LENGTH OF LABOR PRIOR TO PERFORMANCE OF PREVIOUS SECTION

HOURS OF LABOR	TOTAL SCARS	RUPTURED	
		NO.	%
No labor	197	23	11.7
0- 9	69	9	13.0
10-19	89	5	5.6
20-29	60	5	8.3
30-39	20	3	15.0
40 or more	26	3	11.5
Unknown	21	0	0
Grand total	482	48	10.0

TABLE VIII. INCIDENCE OF DISRUPTION OF CESAREAN SCAR IN RELATION TO WEEK OF GESTATION IN WHICH PREVIOUS SECTION WAS PERFORMED

WEEK OF GESTATION	TOTAL SCARS	RUPTURED	
		NO.	%
Less than 36	42	5	11.9
36	24	2	8.3
37	36	3	8.3
38	67	15	22.4
39	69	5	7.2
40	132	12	9.1
41	39	4	10.3
42 or more	47	2	4.3
Unknown	26	0	0.0
Grand total	482	48	10.0

The highest incidence of rupture occurred in the classical type although these cases comprised only 12.5 per cent of the total scars that ruptured.

Rupture of the lower segment was most common in patients who had no labor (or labor of less than 9 hours) and labor of more than 30 hours' duration at the time of primary section (Table VII), and in those in whom the previous section was performed prior to the thirty-ninth week of gestation (Table VIII). In these patients, the lower segment was either poorly developed (as a result of no labor or inertial type of labor) so that the incision may not have been limited to this segment or the relative thickness of the lower segment at this time favored poor healing (as discussed in the section on "Technique").

Indications for Primary Section.—Table IX shows that the highest incidence of rupture occurred when the primary section was performed for antepartum hemorrhage and fetal distress. These are considered by many to be a nonrepetitive indication permitting vaginal delivery in subsequent pregnancies.[4, 10 11] Factors probably responsible for poor scar formation in these instances are suture technique in the face of bleeding, damage to the myometrium due to interstitial hemorrhage, and/or the relative thickness of the myometrium (see "Technique").

TABLE IX. INCIDENCE OF DISRUPTION OF UTERINE SCAR IN RELATION TO INDICATION FOR PREVIOUS CESAREAN SECTION

INDICATION	TOTAL SCARS	RUPTURED	
		NO.	%
Cephalopelvic disproportion			
No labor	29	2	6.9
Labor	144	9	6.3
Uterine inertia	69	7	10.9
Toxemia	35	1	2.9
Abruptio placentae	26	6	23.1
Placenta previa	22	3	13.6
Fetal distress	15	3	20.0
Elective*	52	1	1.9
Previous section	90	16	17.8
Grand total	482	48	10.0

*Elective includes diabetes, previous myomectomy, valuable baby, and abnormal position.

TABLE X. INCIDENCE OF DISRUPTION OF CESAREAN SCAR IN RELATION TO THE NUMBER AND TYPE OF SCARS

NUMBER OF SCARS	TOTAL CASES	RUPTURE OCCURRED DURING SUBSEQUENT DELIVERIES OF VIABLE INFANTS			
		FIRST	SECOND	THIRD	FOURTH
One scar	327	29	0	0	0
Two similarly placed scars	47	2	6	0	0
Four similarly placed scars	2	0	0	0	1

MIXED SCARS		TOTAL CASES	SCAR RUPTURED	
PRIMARY SCAR	REPEAT SCAR		TRANSVERSE	VERTICAL
Transverse	Vertical	9	0	3
	Transverse	1	0	1
	Tertiary vertical			
Vertical	Transverse	5	3	1
	Classical	3	0	0
Classical	Transverse	6	2	0
Unknown	Transverse	1	0	0
	Unknown			
	Tertiary transverse	1	0	0

Parity.—The majority of the patients in this study had 2 pregnancies, and the initial scar was found ruptured in 32 (Table X). In patients with more than 2 pregnancies the influence of parity could be readily studied when the scars were of different types. In these "mixed scars," the more recent one was more liable to rupture.

Location of Placenta.—The implantation of the placenta over the previous uterine incision favors disruption if there is invasion of the myometrium by trophoblastic elements. This was seen in one instance of scar dehiscence and that was in a classical incision.

Technique.—Technique, per se, is probably the most important single factor determining the future integrity of any uterine scar. This is most difficult to evaluate from the available data, and poses several questions: Does the type of closure of the uterus influence the incidence of rupture? Is it important to know the technique of the previous surgeon?

Regardless of the method or material employed to close the uterine incision, the sutures used differ from those employed elsewhere in that they serve a dual purpose—coaptation and hemostasis. To secure hemostasis, larger amounts of tissue are included in each suture than are necessary for approximation. This not only prevents proper coaptation, but also increases tissue necrosis by strangulation. Likewise, the need for extra hemostatic sutures also disturbs proper coaptation and tends to increase tissue necrosis. These latter sutures are rarely recorded in the operative notes.

Poor hemostasis can lead to hematomas within the wound. This may result in an area of increased fibrosis and broadening of the scar, or a partial or complete separation of the edges of the uterine incision. The latter was graphically demonstrated by a recent case in which there was a sudden gush of dark red blood and clots on the fifth postoperative day. Exploration within the uterus disclosed a complete separation of the incision in the transverse lower segment and a marked disparity in thickness of the edges.

Excessive blood loss at the time of operation, as judged by the record of blood replacement, regardless of the primary indication for section, results in an increased incidence of scar rupture (Table XI). This is probably a result of poor wound hemostasis and/or excessive tissue necrosis from multiple hemostatic sutures.

TABLE XI. DEHISCENCE OF UTERINE SCAR IN SUBSEQUENT PREGNANCIES IN RELATION TO BLOOD REPLACEMENT DURING PREVIOUS CESAREAN SECTION

BLOOD REPLACEMENT	INDICATION FOR PREVIOUS SECTION						TOTAL		
	ANTEPARTUM HEMORRHAGE			OTHER					
	TOTAL CASES	RUPTURED		TOTAL CASES	RUPTURED		TOTAL SCARS	RUPTURED	
		NO.	%		NO.	%		NO.	%
No blood	18	5	27.8	294	21	7.1	312	26	8.3
One unit	13	1	7.7	83	15	18.1	96	16	16.7
Two units	17	3	18.2	29	3	10.3	46	6	13.0
Unknown	0	0	0.0	28	0	0.0	28	0	0.0
Grand total	48	9	18.8	434	39	9.0	482	48	10.0

When the uterine incision has edges of unequal thickness it is difficult to approximate them so that the corresponding components are in apposition. This is true not only of transverse incisions made at the junction of upper and lower segments, but also in vertical incisions that extend into the corpus. A similar situation is present when the incision is in a relatively thickened myometrium. This poor approximation results in disruption of direct continuity of the muscle fibers in that area, increases the possibilities of dead space, and

may result in poor scar formation. This weakness, and the increased bleeding from a thick myometrium, probably account for the greater incidence of disruption in repeat section scars than in primary section scars, and also in women whose primary section was performed prior to the onset of labor. It is important in repairing the incision that the endometrium be inverted into the uterine cavity and not everted into the myometrium. Eversion of the endometrium may favor endometriosis or fistula formation with resultant weakness of the scar. This is most apt to occur in upper segment incisions.

Some authors[1, 12] have stated that knowledge of the previous surgeon's technique is essential to determine the mode of delivery in subsequent pregnancies. This study does not permit an evaluation of this statement. It is our personal opinion, however, that the technique employed in each individual instance is more important in future appraisal of the scar than a mere knowledge of the surgeon's ability or qualifications.

Healing Power.—It is almost impossible to assess the healing power of any individual. The nutritional status of the patient is a very important factor in wound healing, yet the incidence of rupture reported herein was similar for ward and private patients. This is due to the excellent nutritional status of the ward patient in this community.

The increased level of corticosteroids present during pregnancy may delay adequate healing and be partially responsible for the higher incidence of dehiscence of abdominal wounds, following cesarean section than following laparotomies for benign gynecological conditions. Two of the 3 patients with abdominal wound dehiscence in this series were found to have rupture of the uterine scar in their subsequent pregnancies. In one of these, the rupture of the scar was incomplete and, despite adequate repair, it was found to be completely ruptured (in the lower half) in the next pregnancy.

Symptoms and Findings.—The term "silent rupture" adequately describes this condition. The presence of pain and/or tenderness in the region of the scar is a poor indicator of its integrity. Most pregnant women will have these symptoms (in some degree) in the last trimester especially, when the lower pole of the uterus is palpated. When repeat section is done for these symptoms, it is rare to find a defective scar. Vaginal bleeding with or without these symptoms prior to the onset of labor, however, may be associated with impending or actual rupture. Emergency repeat section for these symptoms confirmed the preoperative diagnosis of scar dehiscence in only 3 of 12 cases.

Comment

A retrospective study of uterine scar integrity is valueless because it depends upon the accuracy of chart records. Most operators recognize silent rupture, but because of its benign nature, or a false pride, they rarely note it in the operative report. Even when recorded, it is rarely included in the diagnosis on discharge. As a result, this entity cannot be catalogued in the Record Room. This situation became apparent to us in 1952 when a study of the general subject of rupture of the uterus was initiated. Only 3 cases of rupture of a cesarean scar were indexed in our institution from 1932 to 1952. All were symptomatic ruptures of classical scars. A prospective study was instituted, therefore, in 1953 to determine the actual incidence.

The determining factor in recognizing integrity of the uterine scar is the appearance of the scar and not the presence or absence of symptoms. The accurate recording of this observation[13] will of necessity result in a higher incidence of rupture than is generally reported in the literature and will more closely represent the true picture.

Most dehiscences are conceived in the operating room when the uterus is repaired, and they develop during the puerperium. The ensuing pregnancy, in these cases, merely accentuates the pre-existing defect. This concept is substantiated by the appearance of the scar at the elective repeat section and also by Baker's[14] observations from x-ray hysterography of postsection uteri.

The prime function of the bladder flap in low cesarean section was to prevent peritoneal soilage. It now appears that it has an additional function, namely, the prevention of symptomatic rupture. In many cases of silent rupture only the overlying bladder and its peritoneal reflection maintained the products of conception within the uterine cavity. In others, the posterior wall of the bladder was adherent to the separated edges of the uterus. In this manner it bridged the defect and formed an integral part of the anterior uterine wall.[15] If, during labor, this defect is extended, the bladder most likely will be lacerated.

Healing power and surgical technique are the most important factors in determining the integrity of the cesarean section scar. Neither can be accurately evaluated or measured from available data or knowledge of the previous surgeon.

There would be no controversy as to the handling of post-cesarean section patients in subsequent pregnancies if the behavior of the scar could be predicted. The present analysis discloses that the criteria employed are largely empirical. These factors, namely, an afebrile postoperative course, type of incision, knowledge of the previous surgeon, nonrepetitive indications, and absence of symptoms, do not guarantee a scar that will withstand labor.

There is also wide agreement that all symptomatic or asymptomatic uterine ruptures prior to the onset of labor will not be obviated by the mode of subsequent delivery. A thorough analysis of symptomatic rupture prior to the date of elective repeat section reveals that such ruptures almost invariably occur in previous classical scars.[2, 9, 11, 16, 17] This is also true in our institution for there have been only 3 symptomatic ruptures in the past 25 years, and all occurred in previous classical scars with one maternal death. In the past 10 years there have been no symptomatic ruptures, and the incidence of classical incisions has been less than 5 per cent. It is obvious that if the classical section is eliminated, except in rare instances, this catastrophe, with its attendant high fetal and maternal mortality, could be reduced to a minimum.

Prior to labor most defective or ruptured lower segment scars are asymptomatic. There is little doubt that some will withstand labor, while others will progress and become symptomatic and have serious sequelae.[17] Those who favor subsequent vaginal delivery are cognizant of this possibility, and require the operating room to be prepared for this emergency. In addition, they advocate a thorough exploration of the uterine cavity immediately following delivery. Symptomatic rupture during labor will usually require hysterectomy, but an asymptomatic rupture found at repeat section can be repaired and the uterus conserved. Following vaginal delivery, if asymptomatic rupture is discovered, it is generally not repaired. Occasionally it may serve as a portal of entry for bacteria[2] or this weakened area may extend and produce symptomatic rupture during the course of a future pregnancy or labor, with possible laceration of bladder and/or ureters.

Conclusion

From this discussion, it is apparent that there is no method to ascertain the integrity of a cesarean section scar or predict its behavior during labor. Since the maternal risk is less[18, 21] and the fetal risk no greater[22, 23] (Table

XII) with repeat cesarean section than with subsequent vaginal delivery, we shall continue, for the present, to adhere to the dictum, "once a section always a section."

TABLE XII. PERINATAL LOSS IN 482 REPEAT CESAREAN SECTIONS

SIZE OF INFANT	INDICATION FOR REPEAT SECTION	CAUSE OF PERINATAL DEATH			
		ANTEPARTUM	HYALINE MEMBRANE	CONGENITAL ANOMALY	TOTAL INFANT LOSS
2,500 or more grams	Previous section	-	3	1	4
	Diabetes mellitus	1	1	-	2
	Abruptio placentae	2	-	-	2
Less than 2,500 grams	Previous section	-	2	-	2
	Premature labor	-	4	-	4
	Placenta previa	-	1	-	1
	Grand total	3	11	1	15
	Total viable infants delivered			485	
	Loss of viable fetuses			3.1%	

Summary

1. Four hundred three consecutive repeat cesarean sections in patients with 482 scars have been reviewed. There were 48 ruptures, of which 22 were in previous transverse incisions, 20 in vertical incisions, and 6 in classical. The incidence of rupture in transverse scar was 8.3 per cent, in vertical 12.9 per cent, and in classical 18.2 per cent.

2. The two most important factors for evaluating scar potentiality, namely, surgical technique and healing power of the patient, cannot be ascertained from all available data.

3. An afebrile postoperative course does not guarantee a good scar, nor a febrile course indicate a poor scar.

4. Most defective scars develop during the puerperium of the previous pregnancy, and are accentuated by the present pregnancy.

5. The operative record should include the number of special sutures required for hemostasis. This may serve as an aid in evaluating the integrity of the scar in future pregnancies.

6. Symptomatic rupture of a previous scar during pregnancy almost invariably occurs in the classical type of incision. Lower segment scars rarely produce symptomatic rupture prior to labor.

7. Elimination of the classical incision will minimize the occurrence of symptomatic rupture prior to the anticipated date of repeat section.

8. There is no means of predicting accurately the behavior of a uterine scar during the course of a subsequent pregnancy.

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INDICATIONS FOR HYSTERECTOMY IN POSTPARTUM HEMORRHAGE

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HYSTERECTOMY as treatment of severe postpartum hemorrhage is a radical and undesirable procedure. Whether it is indicated in these cases is an extremely difficult decision to make, but even more important is determination of the appropriate time to undertake such a procedure, as too often this operation is performed only as a last resort when the patient's condition is too critical to withstand the risk of operation and the effects of anesthesia. Yet, in reviewing any series of deaths from postpartum hemorrhage, one cannot help but ask: "Could hysterectomy have saved these lives?" Deaths from hemorrhage are either preventable or have preventable factors,[1] and postpartum hemorrhage has been said to be "the most menacing, most deadly and most preventable" of all the hemorrhagic threats to the parturient.[2]

In an attempt to determine the various etiological factors responsible for uncontrollable postpartum hemorrhage necessitating hysterectomy, the emergency hysterectomies performed at the Millard Fillmore Hospital in the past 5 years were reviewed and the findings in this series are reported here.

From Jan. 1, 1952, to Dec. 31, 1956, 10 emergency hysterectomies were performed primarily to control postpartum hemorrhage. Two of these were done at the time of cesarean section, 5 in the immediate postpartum period, and 3 in the late puerperium. During this time there were 24,642 deliveries; thus the incidence was one hysterectomy in 2,462 deliveries.

Subtotal hysterectomy was done in 9 cases, and total hysterectomy in one. There was no maternal death in this series; there were 3 stillbirths and 2 neonatal deaths.

It might be mentioned at this point that in the 5 year period covered by this report there was one maternal death from hemorrhage. This patient went into profound shock and died before any treatment could be instituted.

The 10 cases in this series are summarized in Table I. The patients ranged in age from 24 to 36 years. They were all multiparas. Seven patients were at term and 3 were in the thirty-sixth to the thirty-eighth week of gestation. There was no case of prolonged labor. Five patients were delivered by low forceps, one was delivered spontaneously, and 4 were delivered by cesarean section.

The clinical and pathologic findings in this series are shown in Table II.

Etiological Factors

Placenta Previa and Placenta Accreta.—Kistner, Hertig, and Reid[3] reported 9 cases of simultaneously occurring placenta previa and placenta accreta. According to Greenhill,[4] a large percentage of cases of placenta previa

will show evidence of placenta accreta if all such placentas are submitted to extensive microscopic examination. There were 2 such cases in the present series; in both the diagnosis was verified histologically.

Either one of these conditions can cause severe postpartum hemorrhage. In the series presented by Cosgrove,[5] Dyer and associates,[6] Dodek and co-workers,[7] and Bryant,[8] placenta previa as well as placenta accreta was among the indications for hysterectomy for postpartum hemorrhage. Greenhill[9] is of the opinion that postpartum hemorrhage in placenta previa is usually due to a laceration. The extreme vascularization of the lower uterine segment and cervix, due to the low implantation of the placenta, permits every tear to bleed profusely.

Placenta accreta is rare.[10] Bleeding in this condition occurs in the partial type. The treatment of choice is hysterectomy.

The 2 patients in the present series (Cases 1 and 2, Table I) who were in this category bled immediately following cesarean section. Placenta accreta was not suspected in either case; the diagnosis was established only on pathologic examination. It is interesting that in Case 1 there had been a previous cesarean section, and at the time of operation a rupture of the lower uterine segment, through which part of the placenta protruded, was found. Both patients failed to respond to conservative medical therapy, consisting of blood, oxytocics, uterine massage, calcium gluconate, and vitamin K, carried on for 3 to 3½ hours.

Rupture of the Uterus.—Rupture of the uterus, according to Cosgrove,[5] heads the list of indications for emergency hysterectomies done post partum or at the time of cesarean section. In our series, there were 2 cases of ruptured uterus. The first patient (Case 1) was described in the previous section. The second patient (Case 3) had a traumatic rupture caused by the Holmes uterine packer. Labor was induced in this patient by intramuscular Pitocin in repeated small doses, because of a suspected premature separation of the placenta. At delivery the placenta was found to be implanted in the lower uterine segment. The usual conservative measures (blood, oxytocics, and uterine massage) failed to stop the bleeding: therefore, a uterine pack was inserted with the Holmes packer. Shortly thereafter she was bleeding through the pack. At hysterectomy a rupture was found on the left side of the lower uterine segment.

This case will further support Greenhill's statement that the increased frequency of postpartum hemorrhage in placenta previa or low-lying placenta is not due to atony, but rather usually to a laceration. Whether or not induction of labor with Pitocin was a contributing factor in causing the initial hemorrhage in this case one cannot say.

Atony of the Uterus.—The causes of hemorrhage from atony may be grouped under general and local factors. Among the general causes postulated, exhaustion from prolonged labor, successive labors, and some familial tendencies are the most common. There are many local causes, chief among them being overdistention of the uterus, a large baby, abruptio placentae, sudden emptying of the uterus, abnormal shape of the uterus, distortion by tumors such as myomas, cesarean section and myomectomy scars, and a retained placenta or thick layer of decidual tissues. In the present series four cases may be classified under this heading.

Couvelaire uterus: This condition, per se, is not necessarily an indication for hysterectomy. Hysterectomy will be determined by the response of the uterus to manual stimulation or injection of oxytocics. In the period of time covered by this study we found only 2 cases of Couvelaire uterus in which hysterectomy had to be resorted to.

TABLE I. SUMMARY OF 10 CASES OF POSTPARTUM HEMORRHAGE TREATED BY HYSTERECTOMY

CASE NO.	AGE	PARITY	LENGTH OF GESTATION (WEEKS)	DURATION OF LABOR (HOURS)	DELIVERY	HEMORRHAGE		MEDICAL TREATMENT	DIAGNOSIS		OUTCOME OF INFANT
						ONSET	DURATION		CLINICAL	PATHOLOGIC	
1	25	iv	37	–	Cesarean section	2 hours preadmission, immediately postoperatively	3 hours	Blood 6,500 c.c.; oxytocics; uterine massage (3 hours)	Placenta previa, central; ruptured old scar; severe postpartum hemorrhage	Placenta accreta	Neonatal death
2	36	vi	37	–	Cesarean section	2½ hours preadmission, immediately postoperatively	3½ hours	Blood 2,500 c.c.; oxytocics; uterine massage (3½ hours)	Placenta previa, central; severe postpartum hemorrhage	Placenta accreta	Neonatal death
3	35	iii	40	9 (induced)	Low forceps	30 minutes post partum	2½ hours	Blood 3,000 c.c.; uterine packing; oxytocics (2½ hours)	Low-lying placenta; traumatic rupture of uterus; severe postpartum nemorrhage	Laceration of myometrium	Stillbirth
4	34	v	40	5	Low forceps	Immediately post delivery	2 hours	Blood 6,000 c.c.; oxytocics; uterine packing (2 hours)	Uterine atony; severe postpartum hemorrhage	Uterus of pregnancy	

5	27	iv	40	5	Low forceps	Immediately post delivery	3 hours	Blood 4,000 c.c.; oxytocics; fibrinogen, 3 Gm.; Levophed; uterine packing (3 hours)	Uterine atony; severe postpartum hemorrhage; hypofibrinogenemia	Uterus of pregnancy	
6	35	iv	40	8	Cesarean section	Approximately 2 hours preceding cesarean section and during cesarean section		Blood 8,000 c.c.; oxytocics; fibrinogen, 6 Gm.	Complete premature separation of placenta; Couvelaire uterus; severe hypofibrinogenemia; toxemia	Couvelaire uterus	Stillbirth
7	27	iii	40	–	Cesarean section	1 hour preadmission. Shock on admission		Blood 4,500 c.c.	Couvelaire uterus	Couvelaire uterus	Stillbirth
8	24	ii	38	4 (induced)	Low forceps	7 days post partum	5 hours; 3 hours after curettage	Blood 4,000 c.c.; oxytocics; curettage; uterine packing (5 hours)	Delayed postpartum hemorrhage; placenta accreta	Noninvolution of placental site	
9	34	ii	40	8	Low forceps (spinal anesthetic)	6 days post partum	4 hours	Blood 5,000 c.c.; oxytocics	Delayed postpartum hemorrhage due to uterine fibroids	Noninvolution of placental site	
10	34	iv	40	6½	Spontaneous (spinal anesthetic)	5 days post partum	6 days	Blood 1,500 c.c.; oxytocics; hormones	Delayed postpartum hemorrhage	Noninvolution of placental site	

TABLE II. CLINICAL AND PATHOLOGIC FINDINGS IN 10 CASES

CLINICAL AND PATHOLOGIC DIAGNOSIS		NUMBER OF CASES
Placenta previa and placenta accreta (rupture of section scar in Case 1)		2
Rupture of uterus		2
Previous cesarean scar, with placenta previa and placenta accreta (Case 1)	1	
Traumatic	1	
Atony of uterus		4
Couvelaire uterus (acute hypofibrinogenemia and toxemia in Case 6)	2	
Cause unknown (concomitant hypofibrinogenemia in Case 5)	2	
Noninvolution of placental site		3

Both patients (Cases 6 and 7) manifested the classic clinical signs and symptoms of severe premature separation of the placenta with concealed hemorrhage and shock. The patient referred to in Case 6 had severe pre-eclampsia, and when signs of premature separation of the placenta became evident acute hypofibrinogenemia also developed. Whole blood and fibrinogen were administered. In both patients the cervix was thick, rigid, and undilated, so cesarean section was performed. Both uteri had the classic appearance of Couvelaire uterus. In both patients the uterus failed to respond to manual or Pitocin stimulation, and bleeding was profuse in both cases.

Atony without demonstrable cause: In 2 patients in this series (Cases 4 and 5) no definite clinical or pathologic cause of the hemorrhage could be demonstrated. Both patients were treated by uterine packing in addition to whole blood, oxytocics, and other supportive measures. One patient (Case 4) also received chloroform. Just what role this agent and the uterine pack played in the causation of the hemorrhage is difficult to determine. The other patient (Case 5) had a blood fibrinogen level of 123 mg. per 100 c.c. The sample for fibrinogen determination was taken after the patient had already lost considerable blood and was in shock. Since none of the more common conditions usually associated with hypofibrinogenemia was present, we are more inclined to believe that the defibrination in this case was secondary to the sudden, profuse hemorrhage. As a further evidence that the bleeding was due to the atony and not the hypofibrinogenemia, at the time of operation the incision in the abdominal wall did not bleed excessively despite continuous uterine bleeding.

Noninvolution of the Placental Site.—In 1955 Gainey, Nicolay, and Lapi[11] wrote an excellent paper on the subject of noninvolution of the placental site. Of their 24 cases of severe postpartum hemorrhage which required active treatment (curettage), 7 presented the clinical picture of noninvolution of the placental site. The histologic findings in these cases could not be differentiated from the normal. All the patients improved with curettage. The pathogenesis of this striking clinical entity is not entirely clear. Myometrial atonia, depriving the vascular structure of conditions favoring localized obliterative changes, is suggested as a possible causative factor.

In the present series there were 3 cases of delayed postpartum hemorrhage in which the clinical and pathologic findings may be classified under noninvolution of the placental site. These 3 cases represented only a very small proportion of all the cases of delayed postpartum hemorrhage during the period covered by this study.

In Case 8, the patient was treated with whole-blood transfusions, oxytocics, dilatation and curettage, and uterine packing. Three hours after the dilatation and curettage she was bleeding through the pack and went into shock for the second time. In the other patients (Cases 9 and 10), dilatation and curettage was not attempted; therefore it cannot be said unequivocally that hysterectomy was the best treatment in these 2 instances. According to Gainey

and associates,[11] the majority of these patients can be cured by dilatation and curettage together with supportive therapy. In their series hysterectomy was not deemed necessary in any case.

Comment

Cosgrove,[5] as well as Dyer and co-workers,[6] found that the most common causes of uncontrollable postpartum hemorrhage necessitating emergency hysterectomy were rupture of the uterus, placenta previa, placenta accreta, uterine atony, and Couvelaire uterus. In the present series of 10 cases of emergency hysterectomy for postpartum hemorrhage, these conditions were responsible in 7 instances, either alone or in combination with other factors. Noninvolution of the placental site was the pathologic finding in one case in which conservative measures, including dilatation and curettage, failed to control the hemorrhage. In these cases it appears that the clinical and pathologic findings comprise legitimate indications for hysterectomy. In the remaining 2 cases, which were diagnosed pathologically as noninvolution of the placental site, whether hysterectomy was definitely indicated may be open to question, since dilatation and curettage was not undertaken first.

Hypofibrinogenemia and other alterations in the blood coagulation mechanism are rare, but should be kept in mind in cases of uncontrollable postpartum hemorrhage. If such defects are present, unless they are diagnosed and corrected, one cannot hope to stop the bleeding. Hysterectomy will not cure these conditions unless there is some primary obstetric cause for the bleeding, as exemplified by the 2 cases in this series. In any event, when the fibrinogen of the blood has been depleted, it should be replaced, regardless of whether or not it is the primary cause of the bleeding.

Noninvolution of the placental site is seldom an indication for hysterectomy. These cases usually respond very well to conservative medical measures or dilatation and curettage, or both.

Hysterectomy has a definite place in the treatment of postpartum hemorrhage. If, after the more common causes of hemorrhage, such as retained placental tissue, cervical and vaginal lacerations, and alterations in the blood coagulation mechanism have been eliminated, vigorous, conservative measures fail to control the bleeding, hysterectomy or ligation of the uterine artery should be done before the patient goes into profound shock. Prolonged waiting might be catastrophic. In these cases of uncontrollable postpartum hemorrhage, it is highly probable that one of the conditions said to be among the most common etiological factors,[5, 6] as discussed, is responsible.

Summary and Conclusions

1. Ten cases of emergency hysterectomy performed at the Millard Fillmore Hospital in the past 5 years for uncontrollable postpartum hemorrhage, immediate or delayed, are discussed.

2. The indications for these emergency hysterectomies were placenta previa in combination with placenta accreta, rupture of the uterus, Couvelaire uterus, atony, and noninvolution of the placental site.

3. Hysterectomy has a definite place in the treatment of uncontrollable postpartum hemorrhage. It should not be done as a desperate measure when the patient's condition is too critical to withstand the operative procedure and the effects of anesthesia. Prolonged waiting might prove catastrophic.

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URETEROLITHOTOMY DURING CESAREAN SECTION*

A Case Report

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THE management of an obstructing ureteral calculus encountered in one of our patients during the thirty-second week of pregnancy focused our attention on the infrequency of this complication and the paucity of information concerning its therapy. The incidence of renal calculus during pregnancy is variably given from 1:852[1] to its complete absence in 15,000 obstetrical admissions.[2] It is truly remarkable that the reported incidence of ureteral calculus in pregnancy is not greater, for many of the etiological factors in stone formation appear to be induced by the pregnant state. These are: alterations of mineral metabolism, "physiologic" ureterohydronephrosis with renal infection superimposed upon stasis, and a high level of circulating estrogens.[3]

The patient, a 32-year-old Puerto Rican had had 10 previous pregnancies; her last menstrual period was May 15, 1955, and the estimated date of confinement Feb. 22, 1956. The tenth pregnancy was concluded in May, 1954, with a low flap cesarean section for central placenta previa resulting in a stillborn macerated fetus presenting by the breech.

The present pregnancy, her first at the Mount Sinai Hospital, was uneventful until the thirty-second week of gestation. At that time the patient was admitted to the obstetrical service with a history of acute left lumbar pain associated with nausea and vomiting for the last four hours. There was no history of frequency, urgency, dysuria, or hematuria. Physical examination showed an acutely ill woman writhing in pain. The patient was afebrile but there was marked left costovertebral angle tenderness. Urinalysis showed 10 to 20 red blood cells per high-power field. Demerol was administered for relief of pain and an intravenous pyelogram done. This revealed a calculus located in the midportion of the left ureter and nonvisualization of the collecting system of the left kidney.

Cystoscopy showed no efflux from the left ureteral orifice. Two catheters were inserted into the ureter, and allowed to remain in place held immobile by a Foley catheter placed in the bladder. The patient was placed on oral tetracycline. The ureteral catheters were kept in for 3 days during which time the patient remained asymptomatic. The catheters were then removed. Twenty-four hours later intravenous pyelography and cystoscopy showed the stone impacted in the lower third of the ureter. Immediate ureterolithotomy was considered but it was deemed wiser, primarily in the interests of the fetus, to reinsert the ureteral catheters. This was successfully done under spinal anesthesia with the establishment of good drainage (Fig. 1).

The patient remained asymptomatic as long as the ureteral catheters were unobstructed. On several occasions the catheters became plugged and the patient complained of left costovertebral angle tenderness, which was readily relieved by irrigation of the

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catheters. A urine culture revealed an Enterococcus sensitive to tetracycline and erythromycin. Erythromycin was then added to the previous antibiotic therapy. During the entire time that the catheters remained in situ, a total of 37 days, the patient was afebrile.

At the thirty-eighth week of gestation the estimated weight of the fetus was 2,900 grams. Because of 8 vaginal deliveries previous to cesarean section, an attempt was made to induce labor and effect vaginal delivery. Induction was unsuccessful. A low flap transverse cesarean section with tubal ligation was done under spinal anesthesia; a 2,600 gram living female child was obtained. With the peritoneal cavity open and the uterus delivered into the wound, the calculus in the left lower ureter was readily palpated, surrounded by considerable periureteral thickening. To avoid immediate peritoneal contamination and future infection from drainage at the site of the ureterotomy, the left leaf of the peritoneum was reflected medially and the ureter approached extraperitoneally. The calculus and periureteral induration were readily located and the stone removed by incision of the ureter. After repair of the ureteral wall a Penrose drain was inserted and led out from the ureterotomy site through a separate incision.

Fig. 1.—X-ray showing left ureteral calculus and indwelling left ureteral catheters.

The indwelling left ureteral catheters became obstructed 36 hours after operation and were removed. Following this, the patient had an uneventful course and was discharged on the twelfth postoperative day. She has been asymptomatic since discharge and the intravenous pyelogram made 6 weeks post delivery showed normal visualization of both upper urinary tracts.

Summary

The precise incidence of ureteral calculi complicating pregnancy cannot be stated. Probably, not infrequently, a pregnant woman develops renal colic and passes a calculus spontaneously, but the episode does not find it way into the obstetric literature. At all events, we can be sure that hospitalization for ureteral calculi during pregnancy is a rare occurrence.

The case just reported points out the need for individualization of therapy. This has been stressed in the literature.[4, 5, 6] When the acute episode took place, the fetus was so premature that temporization was necessary to ensure a viable baby. We were able to prevent renal infection and stasis, maintain good renal function, and by-pass the mechanical obstruction through the institution of specific antibiotic drug therapy and the passage of ureteral catheters. When the period of fetal maturity was reached, and an attempt to induce labor failed, cesarean section was repeated and at the same time a ureterolithotomy performed. We have not encountered a similiar report in the literature.

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FETAL DEATH IN UTERO

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DIPPEL[1] in 1934, analyzed 25,000 consecutive deliveries covering a period of thirty-six years in an effort to find an assignable cause for fetal death prior to the onset of labor. Antepartum fetal death occurred in 306 cases (1.22 per cent). One of his findings was that 75 per cent of the women went into labor within 14 days and 87 per cent within 21 days of the fetal death. This finding is responsible for the concept that prolonged retention of a dead fetus should alert one to the possibility of an abdominal pregnancy. In 1953, a patient at the Kings County Hospital retained a dead fetus for 120 days (49 days beyond her expected date of confinement). Because of suspected "extrauterine pregnancy" a laparotomy was performed. The pregnancy was found to be intrauterine and the patient was delivered by cesarean section. (She had had two previous cesarean sections.) This case stimulated us to review our experience with the retention of dead fetuses.

The present study covers the period from Jan. 1, 1951, through June 30, 1955, and the delivery of 16,057 infants that weighed more than 1,000 grams. Fetal death occurred prior to the onset of labor in 165 instances, an incidence of 1.03 per cent. (Such an incidence is comparable to 1.2 per cent reported by Dippel.)

Racial and Age Distribution.—Seventy per cent of the patients were Negro and 30 per cent were white. This racial distribution is in keeping with that of the clinic population. Though the age range in the study group was similar to that of the clinic (15 to 44 years), the patients with fetal death were significantly older than those who delivered living infants. Only 31 per cent of the study group compared to 54 per cent of the clinic population was under the age of 25. In the presence of such a difference in age distribution it would be anticipated that the older patients would be of higher parity. However, this was not borne out. Table I shows that the study group and the controls were of the same parity.

TABLE I. PARITY OF PATIENTS WITH FETAL DEATH IN UTERO
(Percentage Distribution)

	STUDY GROUP	CLINIC
Nulliparas	24	28
Para i-iv	57	61
Para v plus	19	11

Previous Fetal Salvage.—The concept of a "continuum of fetal loss" is fostered by the two following observations: (1) Two thirds of the patients in the

clinic had had a viable pregnancy in the 36 months preceding the current pregnancy while only one half of the study group had given birth to living infants during the same period of time. (2)Seventen per cent of the study group had had a previous fetal death in utero, which is significantly higher than the 5 per cent incidence for the clinic.

Such findings are in agreement with those of the New York Academy of Medicine's study on perinatal mortality,[2] which demonstrated a pattern of previous stillbirths in women whose current pregnancy terminated with the delivery of a stillborn infant.

Time of Fetal Death.—In order to ascertain, as accurately as possible, when fetal death occurred, both the mother's statement regarding the time she last felt fetal movements and the physician's notation as to when the fetal heart was last heard were recorded. Although a discrepancy was anticipated, the time of fetal death as dated by the patient and by the physician's examination were not significantly different from one another. It appears that shortly after a patient suspects fetal death, she presents herself for medical confirmation.

Retention of a Dead Fetus.—In tabulating the interval from fetal death to the onset of labor, on the basis of the patients' statements, it was found that 90 per cent of the patients went into labor within 14 days; 93 per cent were delivered by the twenty-first day, and only 7 per cent retained the products of conception for more than 3 weeks. As indicated earlier, Dippel's figures for the same intervals of time were 75 per cent, 89 per cent, and 11 per cent, respectively (Table II).

TABLE II. INTERVAL FROM FETAL DEATH TO ONSET OF LABOR
(Percentage Distribution)

	14 DAYS	15-21 DAYS	22 OR MORE DAYS
Dippel	75	14	11
Kings County Hospital	90	3	7

This difference in the two studies may be explained by the fact that 32 per cent of the patients in our series had varying degrees of premature separation of the placenta, and labor usually ensues shortly after this accident or pregnancy is terminated as a therapeutic measure. The 32 per cent frequency of premature separation of the placenta in the study group is significantly greater than the clinic incidence of 1.3 per cent.

In the 9 instances in which the interval from fetal death to delivery exceeded 21 days, one fetus was retained for 120 days and then removed by cesarean section; one was retained for 90 days; 2 for 60 days; and one each for 55, 54, 48, 47, and 39 days. The onset of labor was spontaneous in all but the first of these patients (Table III). This reflects our basic philosophy regarding the management of prolonged retention of a dead fetus. We deem it advisable to refrain from active intervention. Table III shows that the duration of the labor was not unduly prolonged. There were no complications in labor and the deliveries were, in essence, spontaneous. There were no instances of retained placenta nor was there undue postpartum bleeding. Although we saw no increase in postpartum hemorrhage, it has been reported[3] that some patients with prolonged retention of dead fetuses develop defects of the blood-clotting mechanism. It is therefore mandatory to check regularly for the appearance of such deficiencies in these cases. When they are encountered, the therapy should be directed toward their correction and not toward termination of the pregnancy.

Congenital Abnormalities.—It was suspected that abnormal fetuses might be retained for an extended period of time. In this study the incidence of congenitally malformed infants was less than 2 per cent (2 anencephalic monsters)

TABLE III. PROLONGED INTERVAL FROM FETAL DEATH TO ONSET OF LABOR IN 9 CASES

DAYS RETAINED	AGE AT DEATH (WEEKS)	AGE AT DELIVERY (WEEKS)	ONSET OF LABOR	HOURS OF LABOR	INTRA-PARTUM COMPLI-CATIONS	MODE OF DELIVERY	POST-PARTUM HEMOR-RHAGE	BIRTH WEIGHT (GRAMS)	CAUSE OF DEATH	MOTHER		
										AGE	RACE	PARITY
39	33	39	Spontaneous	8	0	Spontaneous vertex	0	1,000-1,500	Unknown	27	Negro	Gravida ii, para i
47	32	40	Spontaneous	11	0	Spontaneous breech	0	1,000-1,500	Diabetes	32	Negro	Gravida iv, para iii
48	33	41	Spontaneous	12	0	Spontaneous vertex	0	1,500-2,000	Unknown	22	Negro	Gravida i, para 0
54	34	41	Spontaneous	6	0	Assisted breech	0	1,500-2,000	Toxemia	32	Negro	Gravida iii, para ii
55	24	36	Spontaneous	4	0	Spontaneous breech	0	1,000-1,500	Unknown	17	Negro	Gravida ii, para i
60	27	36	Spontaneous	15	0	Assisted breech	0	1,000-1,500	Unknown	27	White	Gravida iv, para iii
60	33	40	Spontaneous	16	0	Spontaneous vertex	0	2,000-2,500	True knot in cord	27	White	Gravida v, para iv
90	27	40	Spontaneous	5	0	Spontaneous breech	0	1,000-1,500	Unknown	37	White	Gravida vi, para iv
120*	30	46				Cesarean section	0	1,000-1,500	Diabetes	22	Negro	Gravida iv, para iii

*This patient, preoperatively, was thought to have an abdominal pregnancy.

and neither of these infants was in the group retained for 21 or more days after death. Dippel encountered only 5 instances of congenital malformations in his study.

It does not appear that fetal malformations are associated with death in utero prior to the onset of labor. In all probability, as Dippel stated originally, anomalous fetuses die much earlier in pregnancy than those that are included in a study such as this.

Intrapartum Fever.—Intrapartum fever (temperature elevation to 100.4° F. or more at any time during labor) is present in 4 per cent of the deliveries in our clinic. The patients with fetal death developed this complication more than twice as often (8.5 per cent). This difference is statistically significant and probably consequent upon the presence of nonviable products of conception within the uterus. However, the intrapartum infection in the study group, when actively treated with antibiotic agents, did not predispose the patients to the development of postpartum infection. The number of patients with postpartum infection in the study was the same as the clinic incidence (9 per cent).

Fetal Weight and Presentation.—Sixty-three per cent of the infants weighed 2,500 grams or less, as compared to 12.6 per cent of all infants delivered in the clinic. This finding is in keeping with the fact that fetal death occurred at 36 weeks' gestation or earlier in one half of the patients studied. The presentation of the infants at delivery also reflects the fact that one half of the infants died before the thirty-sixth week of gestation. Vertex presentations are found in the clinic 94 per cent of the time and breech presentations 4 per cent of the time. These presentations occurred in the study group with a frequency of 79 per cent and 13 per cent, respectively.

Cesarean Section.—Of the 165 patients, 20 (12.1 per cent) were delivered by cesarean section. The breakdown on the indications for this procedure was as follows: 3 for central previa, 5 for complete and 6 for partial premature separation of the placenta, one for marginal sinus rupture, one for rupture of the uterus, 3 for previous cesarean sections, and one for a transverse lie. The clinic incidence of cesarean section for the period covered by the study was 4.2 per cent.

Hemorrhage.—Excluding the patients who had antepartum bleeding and those who were delivered abdominally, postpartum hemorrhage (blood loss of 500 c.c. or more) occurred in only 2.3 per cent of the patients. The clinic incidence of postpartum hemorrhage during the same period of time was 2 per cent. Apparently uterine atony to a degree sufficient to cause postpartum hemorrhage is not a major consideration following the delivery of a retained dead fetus; furthermore, since a defective maternal clotting mechanism in association with the retention of a dead fetus is not encountered until the fetus has been dead for at least 4 weeks, hemorrhage on the basis of blood incoagulability is only a remote possibility because the great majority of patients will have been delivered within 21 days following fetal death, as shown by both Dippel and the present study. In Dippel's study the incidence of postpartum hemorrhage was lower than that of the general clinic.

Induction.—Induction of labor was attempted 18 times for reason or reasons other than the fetal death. The techniques were rupture of the membranes or Pitocin infusion or a combination of both; the attempt was successful in 11 cases.

Maternal Mortality.—There was one maternal death in the present study and this occurred in 1951. The patient was a 19-year-old Negro woman, a primigravida, who had a spontaneous rupture of the uterus at term and prior to the onset of labor; she died while being operated upon.

Cause of Fetal Death.—With respect to assignable causes of fetal death, 53 of the 165 cases had to be discarded because information was not complete. Of the remaining 112, premature separation of the placenta was associated with 32

per cent of the deaths; toxemia was second with 21 per cent, and diabetes mellitus was third with 11.5 per cent; prolapse of the umbilical cord was implicated in 5.0 per cent, and erythroblastosis in 3.5 per cent of the cases. There were 3 instances of a true knot in the umbilical cord.

Dippel found that syphilis was the most frequently assigned cause of death. In our study there were no deaths attributed to it, even though 5.4 per cent of the patients had a positive serological test for syphilis during the present pregnancy.

Preventability.—An attempt was made to ascertain how often a fetal death might have been prevented (based on gross deficiencies in care that tended to preclude a successful outcome); in addition, we attempted to assign responsibility in any death that was deemed preventable. The dangers inherent in arriving at such conclusions were borne in mind and every effort was made not to be unduly critical.

A fetal death was classified as preventable if one or more of the following were present:

1. The mother had had inadequate prenatal care. For example:

A 32-year-old Negro woman, para iv, gravida v, Rh positive, Wassermann negative, presented herself for prenatal care on only two occasions in the early months of her present pregnancy. She was known to have diabetes and had been informed of the seriousness of this complication and instructed accordingly. She was next seen on admission to the hospital (April, 1953) in the thirty-sixth week of gestation, in early labor; the fetal heartbeat was not heard. After 7 hours of labor she spontaneously delivered a 4,000 gram stillborn male infant from the left occiput anterior.

2. There had been an error in medical judgment. For example:

A 23-year-old primigravid Negro woman, Rh positive, Wassermann negative, was admitted to the Obstetrical Service of the Kings County Hospital (September, 1951) in the thirty-ninth week of her pregnancy in early labor. She had pre-eclampsia and the fetal heartbeat was not heard. After 16 hours of labor she was delivered by low forceps of a 2,350 gram stillborn female infant from the left occiput anterior under Metycaine saddle block. This patient had been discharged from the hospital with a living fetus 12 days previously, following an 8 day period of hospitalization for mild pre-eclampsia.

3. There had been an error in medical technique. None of the cases could be placed into this category.

4. Any combination of the foregoing.

Table IV shows that we classified 36 per cent of the fetal deaths as preventable. The responsibility was roughly divided equally between the patient and the physician.

TABLE IV. PREVENTABILITY
(Percentage Distribution)

	NOT PREVENTABLE	PREVENTABLE	DOUBTFUL	UNCLASSIFIED	TOTAL
Inadequate prenatal care	6.9	45.0			20.6
Inadequate care and error in medical judgment		13.3			4.8
Error in medical judgment	1.0	40.0	100		15.8
Inadequate care and error in medical technique					0.6
Inadequate care and unavoidable disaster	1.0				0.6
Unavoidable disaster	91.1	1.7		100	57.6
Percentage	61.8	36.4	0.6	1.2	100.0
Total cases	102	60	1	2	165

Summary

1. In a review of 16,057 deliveries at the Kings County Hospital 165 cases of fetal death prior to the onset of labor were found, an incidence of 1.03 per cent.

2. There was no difference between the patient's history and the physical examination with regard to dating the time of fetal death.

3. The patients in the study group had an older age distribution than the clinic population though there was no difference in parity.

4. Seven per cent of the fetuses were retained for 22 or more days; the longest period of retention was 120 days.

5. There was no difference in incidence of postpartum hemorrhage between the study group and the clinic at large.

6. Premature separation of the placenta was associated with 32 per cent of the fetal deaths, toxemia was implicated in 21 per cent, and diabetes in 11.5 per cent; a true knot of the umbilical cord was encountered in 3 instances. In none of these cases was syphilis the cause of death.

7. Thirty-six per cent of the fetal deaths were thought to be preventable; the responsibility was equally divided between patient and physician.

8. There was one maternal death (0.6 per cent) following spontaneous rupture of the uterus prior to labor.

9. The data in this study support the concept of conservative management and abstinence from interference in cases of prolonged retention (more than 21 days) of a dead fetus.

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CONTRIBUTION TO THE ANTENATAL DETERMINATION OF SEX

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FUCHS and Riis,[1] James,[2] and Shettles[3] searched for the presence of "sex chromatin"—Barr's[4, 5] corpuscle—in nuclei of exfoliated cells of the fetus in amniotic fluid sediment and were able to determine the antenatal sex in all cases investigated by demonstrating the typical male or female pattern of cells. Amniotic fluid was collected from women at term by rupture of the membranes for induction of labor, by puncture of membranes bulging in the vagina, by needle puncture of bulging membranes at the time of low cesarean section, before or after the induction of labor, or during the middle of pregnancy from cases for surgical interruption by puncture through the uterine wall, etc. Sex chromatin was investigated in amniotic sediment stained with Giemsa or with modified Papanicolaou or Feulgen methods.

According to authors who have studied amniotic fluid cytology, desquamated cells belong to the vagina,[6] to the oral cavity, or to some part of the urinary tract. Using the method of Coutts and Silva-Inzunza's[7, 8] demonstration of sex chromatin in cell nuclei of fresh unfixed and unstained material observed under the phase-contrast microscope, we investigated the presence of Barr's corpuscle in the nuclei of fetal cells exfoliated in the amniotic fluid.

Technique

Amniotic fluid was obtained by transabdominal needle puncture, by puncture of bulging membranes in the vaginas of women in labor, or by puncture of membranes after hysterotomy during cesarean section.

In one case (Case 11) liquid was obtained by transvaginal puncture of bulging forewaters in a 5½ months pregnant woman with inevitable abortion. If blood comes out after puncture the placenta has been reached; in such cases the needle should be withdrawn and no further attempt made.

Fluid is centrifugated for 10 minutes and fresh unfixed or unstained sediment observed under the phase-contrast microscope. Sex chromatin is counted in groups of 100 cells and the average percentage figured. Most cells found in amniotic fluid sediment are nonnucleated, or the nucleus appears disintegrated. These cells are probably squames from the skin. In those cells that are well preserved and in satisfactory condition for study, sex chromatin is easily identified as a dark, dense, planoconvex, rounded or triangular mass, 0.5 to 1.5 μ in diameter, lying in intimate contact with the inner surface of the nuclear membrane (Fig. 1).

Dispersed nuclear chromatin may appear in clumps in contact with the inner surface of the nuclear membrane. When these clumps are thrown out of focus they are seen to be formed by numerous granules. If not well identified they may be falsely interpreted as sex chromatin and be a source of error in the counts.

TABLE I

CASE	INDENTIFICATION CARD	PUNCTURE	SEX CHROMATIN %	SEX CHROMATIN SEX	SEX OF NEWBORN
1	19996/56	Transabdominal	70.0	♀	Female
2	02196/54	Transabdominal	9.0	♂	Male
3	20114/56	Transvaginal	10.0	♂	Male
4	20163/56	Transvaginal	10.0	♂	Male
5	20229/56	Transvaginal	18.0	♀	Female
6	20295/56	Transvaginal	25.0	♀	Female
7	20299/56	Transabdominal	38.0	♀	Female
8	20422/56	Transabdominal	10.0	♂	Male
9	08893/55	Transvaginal	4.0	♂	Male
10	20432/56	Transabdominal	14.0	♀	Female
11	20486/56	Transvaginal	17.0	♀	Female
12	20559/56	Transabdominal	3.5	♂	Male
13	11455/55	Transuterine	3.0	♂	Male
14	07455/55	Transvaginal	28.0	♀	Female
15	13601/55	Transvaginal	8.0	♂	Male

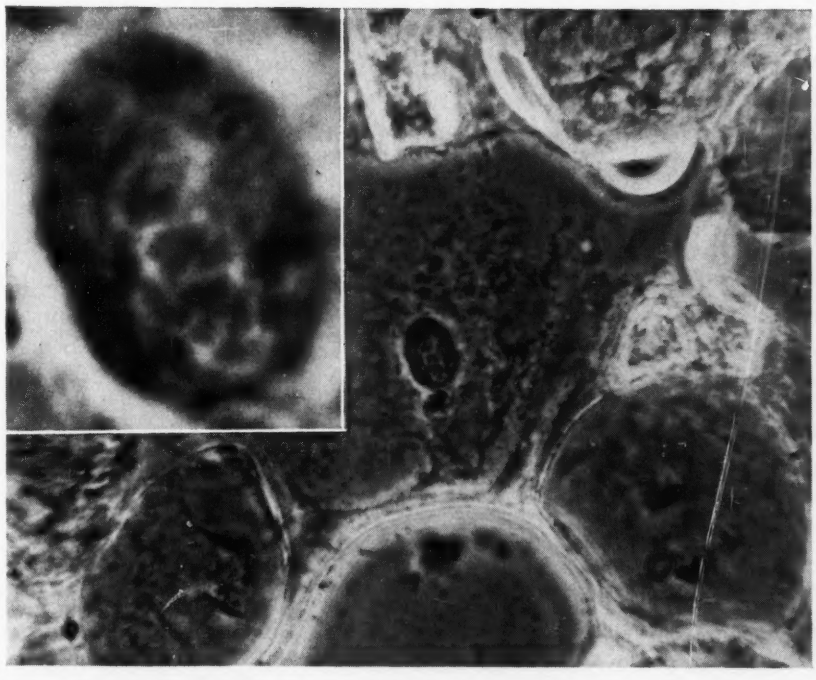

Fig. 1.—Amniotic fluid sediment showing a female nucleus with sex chromatin in a fresh unfixed, unstained preparation (phase-contrast ×900). Inset, enlarged nucleus of same cell showing dense polar mass (sex chromatin) and disperse granular chromatin.

Results

In 15 individuals studied in which the sex was determined, 8 were females and 7 males. In females sex chromatin limits ranged from 14 to 70 per cent; in males from 3 to 10 per cent with an average of 6.5 per cent (Table I).

Comment

Transabdominal needle puncture of the fetal membranes in order to obtain amniotic fluid is not dangerous as demonstrated by authors who have used it. Alvarez and Caldeyro Barcia[9] have, with reasonable care, obtained it from the ninth week up to the end of pregnancy; no harmful consequences to the pregnant woman or the fetus have been recorded.

Staining methods, especially Feulgen's technique, show sex chromatin in a higher proportion of cell nuclei than can be found in fresh preparations. Authors who have determined the sex of nuclei using staining methods find different percentages of sex chromatin. In skin biopsies Moore[4] admitted limits of 1 to 14 per cent in males and 52 to 85 per cent in females; Emery and McMillan,[10] from 4 to 9 per cent in males and from 25 to 54 per cent in females; Tavares,[11] from 1 to 18 per cent in males and from 60 to 80 per cent in females; etc. In the oral mucosa limits also vary according to different authors. Shettles[3] found limits of from 28 to 65 per cent of typical sex chromatin in the cells of amniotic fluid when the fetus is female; other authors who have determined the sex of the cells in amniotic fluid do not give the limits found. Our limits in amniotic fluid ranged from 1 to 10 per cent sex chromatin when the fetus was male and from 14 to 70 per cent when it was female.

These varying limits are apt to introduce confusion if we wish to predetermine antenatal sex by a rapid method. Probably later, when experience is larger, it will be convenient to use our[12] proposed classification of male or female sex, intersex and contrasex, based on the fact that, with respect to nuclear sex chromatin, no human being is 100 per cent male or female. For this reason, like other authors, we count only masses seen to be attached to the innersurface of the nuclear membrane as a step in standardizing sex determination. This is ascertained in fresh preparations by throwing the mass out of focus.

Although the number of cases of antenatal determination of sex by sex determination of cells in amniotic fluid sediment published in the medical literature are few and do not guarantee definite conclusions, the method opens up new fields for investigation.

Conclusions

The sex of the fetus can be rapidly determined antenatally in well-preserved cells in amniotic fluid sediment in fresh unfixed and unstained preparations observed under the phase-contrast microscope. As a means of obtaining this fluid, transabdominal or transvaginal needle puncture of fetal membranes, when done with reasonable care, is not dangerous to mother or child.

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AMNIOTIC BANDS AS A CAUSE OF INTRAUTERINE FETAL DEATH

A Case Report

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AMNIOTIC bands are not rare in pregnancies ending in abortion in the early months. Small threadlike strands have been described connecting the aborted fetus to an otherwise normal-appearing amnion. Instead of threadlike, they may be tent shaped, with the apex attached to the body, head, or ends of the fingers or toes. In early intrauterine existence, due to a more right-angular attachment of the appendages to the body, contact with the amnion might be expected to occur readily to the head and digits.[1] What causes these adhesions can only be conjectured.

Amniotic adhesions and resulting fetal deformities are known to occur in ectopic gestations with more frequency than in normal gestations. In the term or near-term, otherwise normal intrauterine gestation, these amniotic bands are extremely rare. When they do occur, such bands, arising from the amnion, may be free at the other end, or attached to the fetus or to another area of the amnion. Loops may form around portions of the fetus, including digits or portions of extremities, causing corresponding deformities.

These strands may entangle the umbilical cord, causing strangulation of the cord and intrauterine death. Fetal death may occur ante partum, intrapartum, or post partum. One reported case was that of a child born alive at term who died shortly thereafter.[2]

Duncan[2] compiled from the world literature 8 cases of fetal death caused by amniotic strings and added 2 others, one of his own and one of Craven and Geddes[4] in the addendum to his article. The case herewith reported brings the total from the world literature to 11.

The patient was a 19-year-old white girl, gravida i, para 0, who was first seen at Ellington Air Force Base on July 9, 1956. At that time she was approximately 34 weeks pregnant. The last normal menstrual period had been Nov. 13, 1955, and the expected date of confinement was Aug. 20, 1956.

On the last prenatal visit, July 25, the fetal heartbeat was 140, heard in the left lower quadrant, strong and regular. Laboratory tests were completely within normal limits. The Rh factor was negative and the blood type was A.

The patient was admitted on July 30 in active labor. She stated that she had not noticed her baby moving for the past four days and the fetal heartbeat could not be

heard at this time. A macerated stillborn female infant weighing 6 pounds was eventually delivered under pudendal block anesthesia with Trilene, and the placenta was expressed shortly thereafter without difficulty.

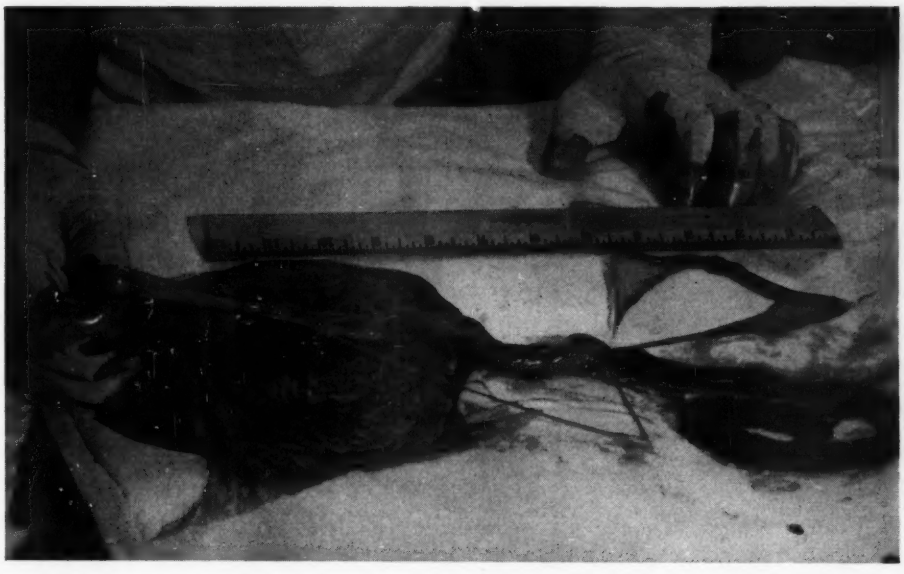

Fig 1.—Amniotic band arises from both cord and placenta and wraps itself tightly around the umbilical cord, causing strangulation.

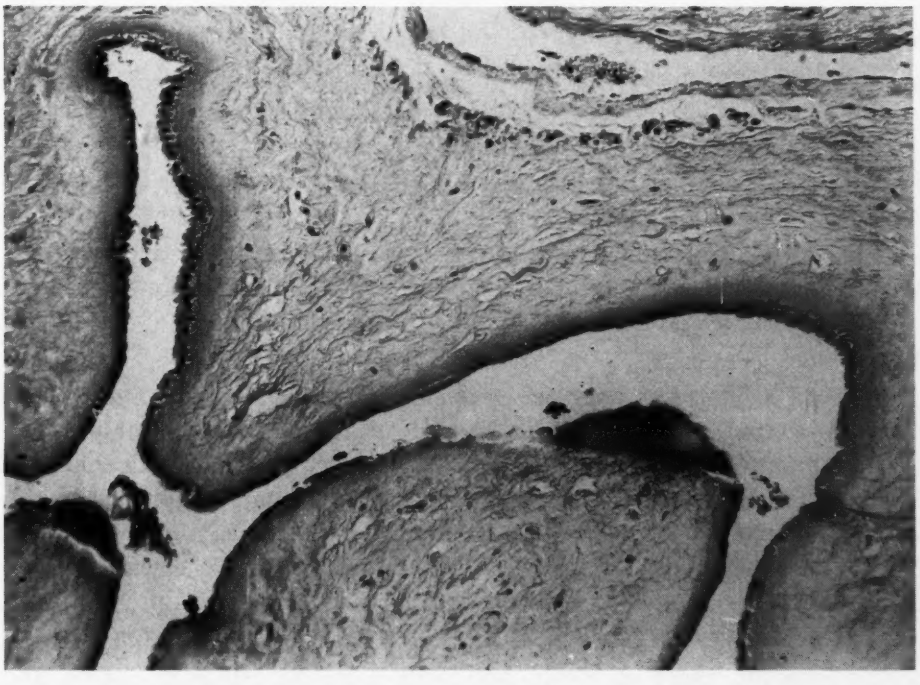

Fig. 2.—Section through the separated amniotic membrane twisting on itself just before becoming a stringlike structure shows amnion cells occurring as a single layer covering one surface. The opposite torn surface contains some scattered chorionic trophoblastic cells.

The umbilical cord presented a brownish-gray discoloration down to a point 4½ inches from its insertion in the placenta, where there was a constriction; on the placental side of this point the cord was normal in appearance (Fig. 1). A strand wrapped on itself in places and in other places appearing as a plain string of tissue was found to be bound tightly around the cord three and one half times. At one end this strand fanned out into what appeared grossly to be amniotic membrane attached to both the placenta and the cord near its placental attachment. From the constriction of the cord, the amniotic band emerged as two strands, each of which fanned out into a paper-thin membrane common to both, but free of any attachment to any other structures.

Pathological Examination.—It was the opinion of Wilson G. Brown, the chief pathologist at Hermann Hospital, that the separated membrane (Fig. 2) had as one surface a single layer of clearly identifiable amnion cells with cuboidal, oval, or slightly irregular pale-blue nuclei and indistinct cytoplasmic borders. The opposing surface showed an occasional plump cell with acidophilic cytoplasm and small darkly stained nucleolus apparently representing a remnant of chorion. It was believed that the amnion had split from the adjacent chorion, carrying with it occasional scattered trophoblastic cells.

Comment

Amniotic bands can be deforming as well as fatal. Traumatic embryonic amputations have been recognized and reported on sporadically since the very early 1800's. There was in all probability knowledge concerning them long before then. Lennon[3] noted that Watkinson in 1825 gave the first report of an intrauterine amputation, but did not record the presence or absence of bands. The left leg had been completely amputated a little above the ankle. The foot was found in the vagina, rather well preserved following the premature birth of the infant at seven months' gestation.

Over the years numerous theories have been postulated as to the etiology of amniotic bands, including: (1) inflammation of the amnion; (2) abnormal disposition of portions of the amnion; (3) maldevelopment of the amnion (developmental, instead of traumatic); (4) environmental influences; (5) dietetic influences; (6) rubella.

Lennon[3] felt that amniotic bands are not adhesions, but are the result of faults in the developing amnion. We agree with him and believe that at least two factors or mechanisms are involved in the formation of these curious strands.

First, an adhesive process takes place between an area of amnion and an area of the fetus, or perhaps another part of the amnion. Over a period of time the amnion is stretched, forming sheets or strings of varying shapes. The etiology of the initial adhesion could be abnormal amnion-chorion attachment to or detachment from adjacent structures: decidua or myometrium in intrauterine pregnancies or adjacent viscera in extrauterine pregnancies. Inflammation in these areas may play a role.

Second, the integrity of the amnion may be disrupted in such a way that it would peel off, twist on itself, and form a string. This might occur as a result of premature rupture of the membranes. Possibly long finger- or toenails might initiate a tear in sites other than the cervical os. These cases are

so rare and are so virtually undiagnosable before delivery that their cause is probably only of academic interest.

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OLIGOHYDRAMNIOS IN RELATION TO ROENTGEN SIGNS OF FETAL DEATH

Case Report

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THE diagnosis of fetal death by the obstetrician or the roentgenologist offers certain definite hazards. This case is presented because the roentgen signs were misleading, due to the presence of oligohydramnios. We hope to alert other radiologists and obstetricians to the pitfalls in attempting to diagnose fetal viability in the presence of this obstetrical complication.

Mrs. E. Y., a 25-year-old para ii, gravida ii, had her last menstrual period on Nov. 2, 1952. In December, 1952, she had some vaginal bleeding which stopped within a few days. On April 16, 1953, she was admitted to the hospital with vaginal bleeding. Although the patient claimed she felt life, no fetal heart sounds were heard. The uterus was smaller than the expected size. The bleeding stopped and she was dismissed on April 19. She continued to feel life and the heart tones were occasionally detectable, but the uterus did not become larger. On April 23 roentgenograms made in the supine and upright positions revealed loss of tone of the fetus, suggesting a nonviable fetus (Figs. 1 and 2). The patient continued to bleed intermittently, with occasional cramps. In May, the uterus had not enlarged noticeably. At this time, she felt life and good fetal heart tones were heard. On May 10 she was readmitted to the hospital with bleeding and contractions. The uterus was no larger than a 4 months' pregnancy. Despite the usual treatment, she started to have regular labor pains on May 12 and 7 hours later expelled the intact amniotic sac and placenta together. The sac was opened and no amniotic fluid except about one tablespoonful of thick mucoid material was found. The baby was alive and cried spontaneously. The source of the bleeding was not found. The baby weighed 1 pound, 11 ounces and was placed in an incubator. On the third day an attempt was made to put a catheter into the baby's stomach for feeding purposes. Shortly thereafter, the baby became cyanotic and died.

Comment

The multiplicity of theories regarding the development of oligohydramnios can be readily compared to the many roentgen signs of fetal death.[1-5] This should only emphasize the lack of reliability of any single criterion in either case. The following are the usual roentgen signs of fetal death: (1) Spalding's[1] sign (overlapping of sutures in absence of labor); (2) flattening of the vault of the skull; (3) asymmetry of the skull; (4) marked curvature or angulation of the spine; (5) indistinct bone markings; (6) failure of the fetus to change position following repeated x-ray exposures; (7) The "halo sign" due to the separation of the scalp from the bony skull; (8) gas in the fetal circulatory system.

Tager[6] offered a new sign based on an extremely simple technique in which the diagnosis of intrauterine death is easily established. In all cases

where the question of fetal death is raised by either the obstetrician or the radiologist, two films are taken. One is a routine anteroposterior projection with the patient supine, and the other with the patient upright, anteroposterior. In the examination of the films, particular attention is directed to the fetal spine, since it offers the easiest landmark. If the roentgenogram in the upright position reveals a complete collapse of the spine into the pelvic area, it is considered pathognomonic of fetal death, constituting the particular sign presented here.

Fig. 1.

Fig. 2.

Fig. 1.—Film in the supine position.
Fig. 2.—Film in the upright position demonstrating fetal collapse.

In our case of oligohydramnios this so-called pathognomonic sign of fetal death was present, yet the fetus was viable. The error was made by misinterpreting the distortion of the fetus and the completely collapsed spine. It is apparent that this sign as well as all the prevailing diagnostic roentgen signs of fetal viability have their exceptions. It is our desire to record the importance of recognizing this complication in the presence of the so-called pathognomonic sign of Tager.

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CARDIORESPIRATORY ARREST IN THE NEWBORN TREATED BY CARDIAC MASSAGE

Report of Two Cases

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CARDIORESPIRATORY arrest with successful resuscitation in children and adults during anesthesia and surgery has been described frequently in recent years.[1-3] Similarly, much has been written concerning resuscitation of infants suffering from asphyxia neonatorum.[4, 5, 11] Reports of cardiorespiratory resuscitation in newborn infants who have been born "dead" as a result of acute anoxia are lacking in the literature. Recently, we have successfully resuscitated two who were born "dead" as a result of anoxia from rupture of the uterus just prior to or during delivery. One child died 36 hours later. These cases are reported here.

CASE 1.—A 38-year-old white woman gravida iii, para ii, was admitted to the Long Island Jewish Hospital at 7:30 P.M. on Jan. 31, 1956, at term and in labor. At 12:30 A.M., she was fully dilated at a plus 3 station. The fetal heart was noted to slow markedly at 1:05 A.M., and it was decided to effect delivery from below. At 1:06 A.M., anesthesia was begun with cyclopropane and at 1:08 A.M., forceps were applied. With the aid of very strong fundal pressure and several strong pulls from below, a male infant was delivered at approximately 1:15 A.M. The infant was noted to be limp, with complete absence of tone or respirations. His color was pale and he was covered with meconium. Momentary palpation of the precordium revealed a very questionable beat. The pharynx was immediately aspirated of some meconium and oxygen was administered with a positive-negative pressure resuscitator with visible and auscultatory inflation of the lungs. The heartbeat was not heard and, therefore, the chest was opened at about 1:20 A.M. through the left fifth interspace. There was no bleeding from the cut skin edges, and palpation of the heart disclosed it to be asystolic, dilated, and flabby. Massage was instituted with the index finger by compressing the heart against the sternum while inflation of the lungs was continued with the mask. After about 1½ minutes, a beat was felt and heart tone quickly improved. Massage was continued for another 30 seconds while the rate increased progressively to about 120 per minute. After another 10 minutes, the infant began to make some respiratory efforts and began to cry 25 minutes after massage. The infant was taken off the resuscitator after about 1 hour at which time he was breathing well, his color was excellent, and he was making spontaneous movements. His birth weight was 7 pounds, 14 ounces.

A diagnosis of rupture of the uterus was made shortly after delivery and immediate hysterectomy was done. The mother made a completely uneventful recovery.

Postoperatively, the infant exhibited twitchings and some mild generalized convulsions but otherwise appeared well. That evening, his temperature rose to 102° F. and he was placed on Thorazine, 2.5 mg. three times a day. The temperature fell to below 100°

but the tremors and convulsive movements continued and, on the second postoperative day, the Thorazine was increased to 5 mg. three times a day. On the seventh postoperative day, medication was stopped and the infant became alert and vigorous. The twitchings disappeared completely within the next 2 weeks. Two electrocardiograms and an electroencephalogram and several chest x-rays taken in the postoperative period were all normal.

At 13½ months of age, he has gained weight to 22 pounds, 5 ounces, and he has apparently developed normally in all respects.

CASE 2.—A 28-year-old Negro woman gravida ii, para i, was admitted at term to Long Island Jewish Hospital on Feb. 7, 1956, at 2:00 A.M. with ruptured membranes and leakage of pale amniotic fluid. The prenatal course was complicated only by hydramnios.

On admission, the cervix was 1½ cm. dilated and thick. The patient was considered not to be in labor. On February 9, at 4:30 A.M., the patient went into active labor. At 10:30 A.M., caput was visible and no cervix was felt on rectal examination. The fetal heart rate was 150 per minute and regular.

A pudendal block with Cyclaine 1 per cent was performed. At 10:35 A.M., anesthesia was started with 6 L. : 2 L. nitrous oxide and oxygen. Good fetal heart sounds were heard by the delivery room nurse. Low forceps were applied and a male infant was delivered at 10:45 A.M. His color was pallid, there were no respirations, and immediate palpation of the precordium revealed no heartbeat. Some very tenacious mucus was aspirated from the pharynx and oxygen administered with a positive-negative resuscitator visibly inflated the chest. Auscultation was done immediately with a stethoscope and when no heartbeat was heard, an incision was made in the left fourth interspace. Attempts to inflate the lungs by the mask were unsuccessful.

After aspirating more mucus from the pharynx, the infant was intubated with a No. 0 Portex endotracheal tube to which the resuscitator was attached. The right forefinger was placed on the heart (pericardium was not opened) which was noted to be flabby and dilated in asystole. Massage was instituted by compressing it with one finger against the sternum. After about 1½ to 2 minutes (4 to 5 minutes after delivery), a heartbeat was detected. Massage was continued while the heart maintained a beat of its own at 50 beats per minute. After another 1 to 2 minutes, the rate accelerated to 126 per minute where it remained. The infant's color improved progressively and in the next ½ to 1 hour, he began to develop muscular tone, spontaneous movement, twitchings, and initiated his own respirations.

About 30 minutes after delivery, the mother suddenly died in spite of resuscitative measures. At autopsy a large rupture of the uterus was discovered with about 2,000 c.c. of blood free in the peritoneal cavity.

Postoperatively, the infant's color remained good with normal respirations for about 20 hours. His chest was clear on auscultation and x-ray and the pulse was 100 per minute. However, the next day, his respirations became jerky and his color became poor. In spite of repeated suction and oxygen, he died at 10:30 P.M. An autopsy was not obtained.

Comment

We are unaware of any previously reported cases of successful cardiorespiratory resuscitation in the newborn. Much of the feeling seems to be that such an attempt is hopeless. Wiggin[1] states: "It is obvious that the newborn who has both respiratory and cardiac arrest has declined to a state that is irreversible." We cannot subscribe to this view. There is ample evidence to show that newborns are less susceptible to anoxia than are adults.[8] Smith[7] cites numerous experiments to demonstrate this point. Pups were shown to withstand oxygen lack 10 times more than adult dogs. Other experiments

show that pups breathing pure nitrogen in which there was no oxygen detectable in the blood were able to survive 30 minutes or more. The reasons given for this increased tolerance to anoxia in the newborn are (1) a decreased cerebral metabolic rate, (2) poikilothermia, and (3) an increased ability to utilize energy via anaerobic mechanisms. The exact length of time that asphyxia can be allowed to persist before irreversible changes will occur is not known. Fletcher[9] gives 5 to 8 minutes as the time limit to correct hypoxia in apneic newborns, while Smith[7] stated that human babies apneic for 10 minutes or more after birth have successfully been revived and developed normally.

The causes of intrauterine asphyxia are legion.[5, 12] Prolonged or recurrent intrauterine anoxia has been implicated as a cause of permanent central nervous system damage.[10-13] Accordingly, we should like to list the requisites necessary before attempting cardiorespiratory resuscitation with the hope of obtaining a normal infant: (1) A trained staff with proper equipment must be on hand in the delivery room ready to act at once. (2) Other than cardiorespiratory arrest, an examination must show the infant to be mature with no evidence of major birth trauma or congenital anomalies. (3) There should be no background of prolonged intrauterine asphyxia or severe systemic disease. (4) Good fetal heart sounds must be heard in the 5 to 10 minute period just preceding delivery.

Pathological and chemical changes occur throughout the body of the newborn subjected to asphyxia.[6] The typical changes of congestion, hemorrhage, edema, and tissue degeneration in the brain are responsible for the transient or permanent neurological sequelae seen as an aftermath of a severe bout of asphyxia. Such gross manifestations as twitchings, convulsions, palsies, spasticities, etc., may disappear as resolution of the acute process proceeds in the brain. On the other hand, more subtle and perhaps latent manifestations, such as character changes, diminished intelligence, emotional afflictions, or epilepsy, have been ascribed to fetal or neonatal asphyxia. At this time, it is impossible to determine whether the infant in Case 1 will be so affected. It remains for more cases to be reported and followed to determine the merit of attempting to salvage this small group of infants heretofore deemed beyond resuscitation.

Summary

1. Two cases of cardiorespiratory arrest in the newborn treated with cardiac massage and resuscitation are reported. One infant survived.

2. The criteria for attempting cardiorespiratory resuscitation in the newborn are listed.

3. The rationale for performing this procedure is presented.

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REPORT OF CYSTIC HYGROMA OF THE NEWBORN INFANT CAUSING DYSTOCIA

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HYGROMA of the neck is not very common and its presence in such proportions as to cause difficulty in delivery of the affected fetus is exceedingly rare. No well-described case of this type of tumor causing dystocia has been detailed, nor does any American textbook of obstetrics mention such a possibility. For these reasons it is believed that the following case should be reported.

The patient, a white gravida i, aged 24 years, was admitted to the Albany Hospital in mild labor on May 27, 1951. The prenatal course had been uneventful, the pelvis was apparently normal, the Rh factor negative. She had elected to deliver her baby, if possible, by the so-called "natural childbirth" method. The first stage, although lasting 24 hours, progressed normally without medication. After 2 hours of strong second-stage contractions with no progress, she was persuaded to allow the baby to be extracted with forceps.

Vaginal examination disclosed what seemed to be a normal-sized head just below the level of the ischial spines in right occipitoposterior position. Manual rotation to an anterior position was unsuccessful. Tucker-McLane forceps were applied and instrumental rotation was attempted, again with no success. In the hope that rotation would be easier if the head could be drawn to a lower level, traction was made, but the blades slipped from the head.

Tarnier forceps were then applied and the head was drawn down almost to the pelvic floor. A right mediolateral episiotomy was done and rotation to an anterior position was rather easily accomplished. The blades were removed, reapplied, and the baby extracted without great difficulty. The cause of the difficult delivery was then apparent, for the baby presented the picture shown in Fig. 1. The duration of the operative procedure was one hour. The baby weighed 7 pounds, 2 ounces. It died 15 minutes after birth. The mother's convalescence was normal, and she was discharged from the hospital on June 3. She has since been delivered of 2 normal boys, one weighing 8 pounds, the other, 8 pounds, 14 ounces.

The pathological report was "a large cystic, soft distending mass extending from the lateral margins of the neck anteriorly." The tumor covered the entire thoracic cage. It measured 17 by 11 by 14 cm. in its greatest diameters. The circumference was 52.5 cm. or 21 inches. The specimen was preserved for demonstration purposes.

Diagnosis: Cystic hygroma of the neck.

Comment

Gross and Goeringer[1] believed that "there is agreement among embryologists concerning the presence of the jugular and other lymphatic sacs in the

human and other vertebrate fetuses. The positions of these structures and the similar anatomical positions of hygromas appear to leave little doubt that a pinching off or sequestration of tissue from one of these embryological lymphoblastic islands or channels gives rise to an endothelium lined lesion which we know as hygroma."

Fig. 1.—Photograph of newborn with cystic hygroma of the neck.

The obstetrical lesson to be learned from this case seems obvious. A more careful vaginal palpation would have revealed the presence of the tumor, and puncture and drainage of the cystic mass would have made the delivery much easier. The value of obtaining pelvic x-rays in patients who have strong contractions without visible progress for 2 hours in the second stage is that they may show tumors of this size or the presence of a deflection attitude, or unsuspected contracted pelvis.

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MANAGEMENT OF POSTPARTUM CONSTIPATION WITH DIOCTYL SODIUM SUCCINATE

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BOWEL management of the patient in the immediate postpartum period has troubled patients and physicians alike for many years. Bowel sluggishness, so common in the last trimester of pregnancy, usually persists in the postpartum period. Frequent use of analgesic drugs in labor, and of narcotics for the relief of afterbirth pains adds considerably to the problem. Also, the patient is faced with the dilemma of continued constipation, or receiving an enema, which may further increase her perineal pain. For many years in this institution, the postpartum patient has routinely received a laxative on the second postpartum day. This has been followed, if the laxative was unsuccessful, with an enema on the morning of the third postpartum day. At least 90 per cent of the patients in this institution have received enemas under this program.

In an effort to alleviate this problem, we undertook a study of the use of dioctyl sodium succinate* for the management of constipation in the postpartum patient. Wilson and Dickinson[1] reported a large series of cases of severe constipation treated with dioctyl sodium succinate. This is a surface active compound employed as a dispersing agent. The compound is inert when administered orally, and acts mainly by lowering the surface tension in the gastrointestinal tract. Water and fatty material mix then with fecal material, resulting in a softer stool. Because dioctyl sodium succinate acts only as a stool softener, Alophen was used in association as a mild stimulant of gastrointestinal motility. When dioctyl sodium succinate was used in therapeutic doses, no irritation of the large intestine was observed.

Two hundred and three successive patients who were delivered on the Obstetrical Service of St. Elizabeth's Hospital were used for this study. This series included primiparous as well as multiparous patients and 13 patients who were delivered by cesarean section. Patients were given a 50 mg. capsule of dioctyl sodium succinate as soon as they were able to tolerate fluids by mouth. Approximately twelve hours later, patients received one Alophen pill together with another capsule of dioctyl sodium succinate. Dioctyl sodium succinate was repeated twice a day for the next two days. Patients were questioned daily as to spontaneous bowel movements and pain in the area of the episiotomy.

The patients appeared pleased with the results of this treatment. Only 13 patients (6 per cent complained of pain in the area of the episiotomies.

*Supplied as Colace by Mead Johnson & Company.

Twenty-five patients had spontaneous bowel movements by the second postpartum day. One hundred and one patients had spontaneous bowel movements by the third postpartum day. Thus, at least 126 patients (62 per cent) did not need enemas. If a patient did not have a spontaneous bowel movement, she was given an enema on the morning of the third postpartum day. The enema was repeated the next morning if necessary. Seventy-one patients (35 per cent) required one enema, and only 5 patients (2.5 per cent) required more than one enema. Of the 13 patients delivered by cesarean section, 2 had bowel movements induced by treatment by the third postpartum day, 9 required one enema, and 2 required two enemas. There were no cases of fecal impaction. Results of the enemas were more satisfactory than when dioctyl sodium succinate was not used.

We feel that dioctyl sodium succinate is a valuable adjunct in the care of the postpartum patient. By elimination of the need for enemas in over 60 per cent of the patients, more time was given to the nursing personnel for the bedside care of the patient. Need for straining at stool was eliminated and patients complained less of perineal pain. No toxic reactions were encountered.

Summary

The effect of dioctyl sodium succinate on postpartum constipation was evaluated in a group of 203 patients. One hundred and twenty-six patients (82 per cent) had spontaneous bowel movements by the third postpartum day. The incidence of pain in the area of the episiotomy was decreased, as patients did not strain at stool.

Dioctyl sodium succinate appears to be a valuable adjunct in the bowel management of the postpartum patient.

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POSTPARTUM SUBPERITONEAL HEMATOMA*

A Case Report

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PUERPERAL hematomas are quite rare, occurring approximately once in 4,000 cases, and large ones only once in 10,000 cases. This complication usually takes place during the descent of the fetus or shortly after delivery; a few cases have been reported to have occurred as late as 14 to 21 days post partum. These late hematomas are attributed to the sloughing of a vessel which had become necrotic as the result of prolonged pressure.

When the torn vessel lies above the pelvic fascia, the hematoma develops above it and gives rise to a rounded tumefaction which projects into the upper portion of the vaginal canal. If the bleeding is not checked it spreads apart the broad ligament and separates the peritoneum from the adjacent tissues; then the hematoma forms a tumor palpable above Poupart's ligament or may invade the renal region and eventually reach the diaphragm.

If treatment is not instituted promptly, the patient usually succumbs to acute anemia or the hematoma may become infected and cause death.

The symptoms are primarily pain and/or blood loss. The pain is that of tearing of the tissues and is excruciating in character.

Treatment.—Laparotomy should be promptly performed once the diagnosis is made, after or with suitable blood replacement; blood clots should be evacuated and hemorrhage controlled by ligature or packing with gauze.

Mrs. D. L., 22-year-old primigravida, was admitted to St. Elizabeth's Hospital in labor on April 20, 1955, at 7:20 P.M. Delivery was accomplished at 2:22 A.M., April 21, by elective forceps. Heavy postpartum bleeding occurred. Packing was inserted in the uterus. A transfusion was given. The episiotomy and second-degree extension were repaired. At 4:45 A.M. the patient was sent to her room. At 5:45 A.M. she became restless and complained of severe suprapubic pain. She was cold and clammy with only slight vaginal bleeding. Plasma and more blood were given. Consultation was called at 8 A.M. More blood was ordered and the patient was taken to the delivery room for a sterile vaginal examination. The packing was removed. A large suprapubic mass was palpated displacing the uterus upward and to the right. The bulging anterior lateral vaginal wall was opened after catheterization. Clots were extracted and the cavity packed with gauze. The patient's condition did not improve and a laparotomy was performed under local anesthesia.

A midline incision was made from the umbilicus to the pubes and a large hematoma was found behind the posterior sheath of the rectus muscles. The clots were removed. The bleeding point was searched for and several oozing areas on the bladder were found. The

*Presented at a meeting of the Chicago Gynecological Society, Feb. 17, 1956.

vaginal packing was removed through the abdomen and Gelfoam was inserted over the oozing areas. A gauze packing was then inserted over this. The peritoneum was opened to make sure that the uterus was not ruptured. The peritoneum was closed. A stab wound was made in the left flank and the end of the gauze packing was drawn through it, for easier removal later. The fascia and skin were then closed. The gauze drain was gradually withdrawn daily and completely removed on the third postoperative day.

On the third postoperative day the rectal temperature was 103° F.

Terramycin was administered intramuscularly twice a day. The temperature subsided gradually to normal on the ninth postoperative day and the patient was dismissed on the tenth day. Her postpartum recovery was otherwise uneventful.

She received a total of 5,000 c.c. of blood.

SYNTHETIC OXYTOCIN

Critical Evaluation in Labor and Post Partum

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THE identification and synthesis of the oxytocic fraction of the pituitary gland secretion by du Vigneaud[4, 5] and Tuppy[14] constituted a milestone in the annals of biochemistry. Pharmacological studies[6, 12] have demonstrated the similarity between the natural and the synthetic oxytocin. Limited clinical trials of synthetic oxytocin have been undertaken and end results reported.[1, 2, 3, 7] Critical evaluation of the physiological effect of this substance on the human gravid uterus in vivo is the end to which the two studies herein reported are directed.

The methods of study consist of the graphicostatistical cervimetric techniques previously detailed,[8-10] whereby progress of cervical dilatation in labor on a time basis is contrasted statistically with similar data obtained from series of comparable untreated cases. Evaluation of postpartum effect is based on observations made, collected data being compared with that of similar groups of patients serving as controls.[11]

The patients to whom synthetic oxytocin* was administered were all patients in labor at the Sloane Hospital for Women, New York City. Selection was essentially random, the material being given at first to 100 consecutive individuals immediately post partum following the delivery of the placenta, in doses of 10 units intramuscularly. Data on the effectiveness of the drug as an oxytocic, as well as on its possible side effects, were obtained.

Once having been able to demonstrate that we were dealing with a substance with uterotonic action and apparently devoid of significant untoward side effects, we began the second phase of the study. The latter consisted of an attempt to assess its value as an antepartum stimulant for induction and/or augmentation of labor. In all, 236 patients received synthetic oxytocin before and during labor, and it appears from the data reported below that the drug is, within the restricted limitations of its use and applied in the cautious manner to be described, a safe effective oxytocic for clinical use.

*Supplied as Syntocinon, OTS-68, Pharmaceutical Division of the Sandoz Chemical Company, Hanover, N. J., synthesized by the method of Boissonnas.[15]

Postpartum Evaluation

Among the items studied in the series of 100 patients who received the synthetic oxytocin post partum were: blood pressure before and during pregnancy and labor, duration of labor, length of third stage, sedation and anesthesia during labor and delivery, trauma, estimated blood loss and recurrence and degree of nausea and vomiting. In addition, blood pressure and pulse observations at 5 minute intervals for one hour after delivery, ante- and postpartum hemoglobin determinations, and responsiveness of the uterus to the drug were noted.

Data thus derived were compared with data obtained from a recent similar study,[11] wherein a control group was used to evaluate other drugs currently in use and available as postpartum oxytocics at this institution.

The make-up of the group was characteristic of a normal sampling of clinic population with regard to age (26.2 years versus 26.4 years control), parity (1.33 versus 1.39 control), incidence of prematurity (6.0 per cent versus 6.8 per cent control), precipitate and prolonged labors, light and heavy sedation, conduction and general anesthesia, types of trauma, and methods of delivery. These features indicated that differences found, if any, could probably be attributed only to the single variable, namely, the postpartum oxytocic employed.

Of interest was the occurrence post partum of demonstrable uterine atony in only 11.0 per cent of this group. This compares favorably with the incidence of 22.0 per cent in the controls. It is not dissimilar statistically from the incidence of atony following naturally occurring oxytocin and demonstrates the uterotonic efficacy of synthetic oxytocin.

Average estimated blood loss, admittedly inaccurate at best, was less, although of doubtful significance, than that of the control group. Breakdown into somewhat more accurate 250 c.c. increments of blood loss showed 79.3 per cent to have lost less than 250 c.c., 18.5 per cent to have lost 250 to 499 c.c., and 2.2 per cent over 500 c.c. These compare quite well with 58.8, 39.2, and 2.1 per cent, respectively, in the control series, indicating what appears to be somewhat less over-all hemorrhage after the use of the synthetic preparation.

In so far as side actions were concerned, nausea and vomiting occurred in 4.0 per cent, all mild cases. The control incidence had been found to be 4.5 per cent, from which we infer that oxytocin has no emetic action in the dosage used.

Blood pressure elevations (above 140 mm. Hg systolic and 90 mm. Hg diastolic and, if previously elevated, 15 mm. Hg systolic and/or 10 mm. Hg diastolic above the highest previously noted observation) were encountered post partum in 20.0 per cent; 7.0 per cent of these were "significant," i.e., greater than the minimal limits noted above by more than 15 mm. Hg systolic and/or 10 mm. Hg diastolic. This is nearly identical with the over-all frequencies of 15.3 per cent control and 18.7 per cent after natural oxytocin, and "significant" elevations of 10.2 per cent and 11.7 per cent, respectively. These data indicate an apparent absence of pressor action in association with the administration of the drug under surveillance.

No other observable signs or symptoms which could be attributed to the use of the drug were demonstrated in this series.

In summary, this material has illustrated that synthetic oxytocin is effective as a uterotonic agent when used post partum, and that it is devoid of major untoward effects in the dosage used.

Intrapartum Evaluation

Synthetic oxytocin was administered to 236 gravid patients according to the standard infusion method described by Moore and D'Esopo,[13] employing a solution of 7 I.U. of drug diluted in 500 c.c. of aqueous solution of dextrose given by slow intravenous drip. Extreme caution was utilized in adjusting the rate of flow according to the patient's need and the uterine response, in an attempt to simulate clinically normal labor.

The drug was used for induction of labor in 126 patients, and for stimulation of labor in progress in 110. Inductions were elective in 102; indications for the remaining 24 cases included, in decreasing frequency, diabetes mellitus, severe pre-eclampsia, essential hypertension, heart disease, Rh factor incompatibility, myasthenia gravis, and gouty nephritis. The group in which the drug was used after the onset of labor included cases of desultory labor, primary inertia, and secondary arrest of cervical dilatation.

The composition of the group was essentially no different from that of the average clinic population, including 96 (40.7 per cent) primigravidas, over-all average parity 1.3, average age 28.6 years. All of those who were delivered subsequent to the use of the drug had vertex presentations, of which 19.5 per cent were occiput posterior; 110 (51.0 per cent) patients were delivered spontaneously, 90 (41.6 per cent) by low forceps, 8 (3.7 per cent) by midforceps, 2 (0.9 per cent) by version and breech extraction, and 6 (2.8 per cent) by cesarean section. The fetal weight averaged 3,150 grams.

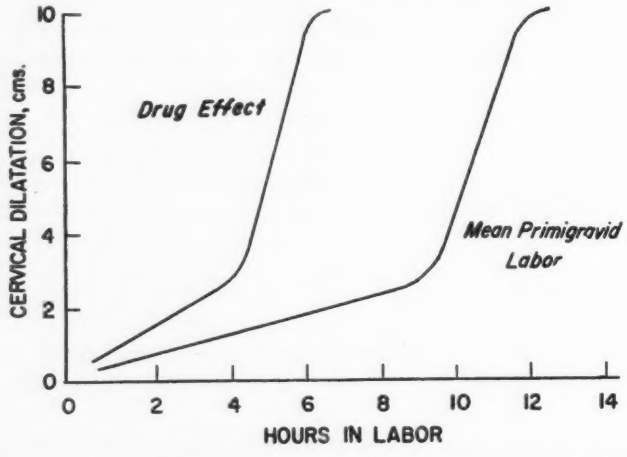

Fig. 1.—Graphic representation of the effect of synthetic oxytocin on the course of labor in 83 primigravidas as compared with an average cervimetric curve (broken line) based on a study of 500 unselected primigravidas.

The total duration of administration of the infusion averaged 4.6 hours, representing a total clinical experience of over 1,000 hours. The average amount of infusion was 210 c.c. (4.2 units of oxytocin), given at an effective rate averaging 12 to 18 drops per minute. The range of duration was 0.2 to 10 hours, of dosage 5 to 500 c.c., and of rate of administration 6 to 40 drops per minute.

There were no maternal deaths and only one perinatal death in the series. The latter no doubt reflects the selectivity of the patient material.

Among the 126 inductions, 109 were successful, the ensuing labors being essentially normal. Where utilized for stimulation of dysfunctional types of labor in 110 patients, the drug was effectual in all but 3 (97.3 per cent effective). The rate of failure, therefore, was 20 in 236 over all (8.5 per cent), or

17 in 126 inductions (13.5 per cent). Twelve of the 17 patients in whom inductions failed were delivered after an interval of 3 days or more following the attempted induction, indicating that they probably lacked the requisite criteria for induction.

Labor in progress was stimulated in the latent phase in 54 and in the acceleration phase in 28, in attempts to shorten already prolonged latent periods in which dilatation had not yet begun or was progressing slowly. The active phase (phase of maximum slope) was augmented in 16 instances in which secondary arrest of dilatation occurred or in which progress was clinically deemed inadequate. The drug was used in the deceleration phase in 10 for similar reasons; and in the second stage in 2. The response to the administration of synthetic oxytocin solution was a normal pattern in all cases except 3, 2 in the deceleration phase and 1 in the second stage. This is especially noteworthy in that subsequent satisfactory progress occurred so frequently.

The cervimetric labor patterns were examined with particular reference to the effect brought about by the drug in question. The duration and the slope of the several phases of the first stage of labor were measured in each case. Data derived thereby are presented in Table I, in which the values cited are the averages for only those portions of labor which followed the use of oxytocin, that is, the "effective" interval. These are compared with similar data obtained from unselected labor cases.[9, 10] The differences, in theory, represent the drug effect. Subjecting the latter to statistical analysis, one may determine their relative significance.

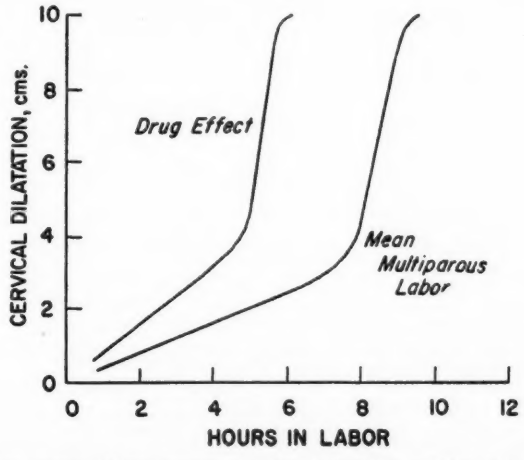

Fig. 2.—The effective mean labor curve produced by the action of synthetic oxytocin on 133 labors of multiparas contrasted with the average of 500 unselected multiparas.

It is found that all phases of labor, when acted upon by oxytocin, are significantly foreshortened in both primigravidas and multiparas, with the exception of the deceleration phase in multiparas and the second stage in primigravidas. In addition, the maximum slope of the active phase of dilatation was significantly more steeply inclined following synthetic oxytocin. Figs. 1 and 2 graphically present these data in primigravidas and multiparas, respectively, contrasting them with average labor curves.

Without consideration for whether or not the results of stimulation are desirable, it is nevertheless apparent that synthetic oxytocin has effective uterotonic action in labor. If comparison is made with data based on a group of "ideal" primigravidas (see Table I), whose labors presented no complicating

features at all and progressed normally without interference, it becomes clear that labor enhanced by oxytocin approaches this allegedly ideal pattern. Statistically, the values are identical except for the significantly short latent phase following oxytocin. The latter strongly suggests that the process of softening and effacement of the cervix, which takes place during the latent phase of the first stage of labor prior to the onset of active dilatation, is markedly speeded.

Examination of those patients only whose labor was induced by synthetic oxytocin provides confirmatory evidence (see Table I). This subgroup consists of 31 primigravidas and 78 multiparas. The inductions in primigravidas exhibit the same significant changes as above noted, namely, that all phases of the first stage are shortened and the maximum slope steepened. The inductions in multiparas again show significantly shortened average latent phase and second stage. The duration of the active phase and the maximum slope, however, although apparently affected in the same manner as in the entire multiparous series, are not significantly altered. Further study may perhaps demonstrate the statistical significance of this aspect of the drug effect.

TABLE I. EFFECT OF SYNTHETIC OXYTOCIN ON LABOR

	LATENT PHASE (HOURS)	ACTIVE PHASE (HOURS)	MAXIMUM SLOPE (CM./HR.)	DECELERATION PHASE (HOURS)	SECOND STAGE (HOURS)
Mean labor in primigravidas*	8.6 ± 0.27§	4.9 ± 0.15	3.0 ± 0.08	0.90 ± 0.05	0.95 ± 0.04
Drug effect, all primigravidas	3.6 ± 0.63‖	3.1 ± 0.24‖	3.8 ± 0.32‖	0.57 ± 0.07‖	0.80 ± 0.07
Drug effect, inductions in primigravidas	3.6 ± 0.88‖	3.1 ± 0.29‖	3.2 ± 0.38‖	0.49 ± 0.10‖	0.79 ± 0.13
"Ideal" labor in primigravidas†	7.1 ± 0.28	3.4 ± 0.11	3.5 ± 0.13	0.70 ± 0.05	0.76 ± 0.04
Mean labor in multiparas‡	5.3 ± 0.19	2.2 ± 0.07	5.7 ± 0.16	0.23 ± 0.01	0.29 ± 0.01
Drug effect, all multiparas	3.2 ± 0.21‖	1.9 ± 0.10‖	7.0 ± 0.50‖	0.20 ± 0.04	0.17 ± 0.03‖
Drug effect, inductions in multiparas	2.8 ± 0.21‖	2.0 ± 0.11	7.1 ± 0.71	0.22 ± 0.04	0.19 ± 0.03‖

*Mean labor data based on the graphicostatistical analysis of 500 unselected labors in primigravidas.[9]

†Mean labor data based on 200 selected uncomplicated labors in primigravidas.[9]

‡Mean labor data based on 500 random labors in multiparas.[10]

§Limits denoted by ± indicate standard error of the mean, SE_m.

‖Statistically significant, $P<0.02$, by critical ratio, deviation/$\sigma>2.32$ where σ is the standard error of the difference between means, $\sigma = \sqrt{SE_{m_1}^2 + SE_{m_2}^2}$.

Conclusions

It has been hypothesized[9] that the actions of diverse factors, both exogenous and endogenous, upon the course of labor may be critically evaluated by means of the technique of graphicostatistical analysis. The latter consists of portraying the progression of cervical dilatation on a time basis in a graphic expression. The sigmoid curve which this describes may be divided into phases, the initial limb called the latent phase and the ascending limb or active phase divided into an acceleration phase, a linear phase of maximum slope, and a deceleration phase. These phases may be examined individually as to duration and slope, and data obtained employed for statistical comparisons.

Data characterizing average labor progression, derived from 2 randomly selected series of patients, have been utilized for the purpose of determining

the effect of synthetic oxytocin administered for the induction and/or stimulation of labor in a comparable group of parturients.

It has been determined, and verified by standard statistical methods, that synthetic oxytocin produces a significant foreshortening of all the phases of the first stage of labor in primigravidas. In addition, there is an apparent though insignificant diminution in duration of the second stage. In multiparas, the drug causes reduction in duration of all phases except the deceleration phase. The maximum slope is correspondingly greater in both groups.

The question of whether the effects noted are desirable may be raised. The therapeutic efficacy of changing many desultory or arrested labors into normal patterns is incontrovertible. In so far as its use to induce labor or to stimulate otherwise normal labor in progress is concerned, no untoward side effects were noted in the present study. It should be stressed that the material was administered in a most cautious manner. The rate of administration was regulated by the uterine response elicited so that excessive and potentially harmful stimulation was avoided.

The over-all effect of speeding the normal pattern of labor progress has been equated with a theoretical ideal in all its components except the latent phase. The abnormal contraction of the latter by oxytocin may conceivably cause harm in some way to mother or infant, although this has not been demonstrated. No obvious fetal damage has been seen; nor was there an excessive occurrence of cervical laceration or hemorrhage in labor or post partum. No tetanic contractions were observed, and no unexplained fetal distress was noted.

It appears reasonable to conclude that the use of the uterotonic preparation in labor is safe and effective. The limitations of its use, however, are clear-cut and should be adhered to in practice.

Summary

1. A critical quantitative in vivo evaluation of synthetic oxytocin has been undertaken and is herein reported.

2. Effective action as a postpartum uterotonic agent is demonstrated.

3. When used to induce labor, a failure rate of 13.5 per cent is encountered.

4. In dysfunctional labors, 97.3 per cent effectiveness is noted.

5. The effect of synthetic oxytocin upon the progress of cervical dilatation is determined by graphicostatistical cervimetric analysis.

6. In primiparas, all phases of the first stage of labor are significantly shortened and the maximum slope steepened, the pattern approaching a theoretical ideal.

7. The same changes are seen when the drug is used in multiparas, except for the deceleration phase.

8. No untoward effects are evidenced either in labor or post partum, to mother or infant, when utilized in the cautious manner described.

Acknowledgment is due the Attending Staff of the Sloane Hospital for Women for permission to administer the oxytocin preparation to their private patients, and to the resident and nursing staffs for their enthusiastic cooperation.

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A PRELIMINARY REPORT ON DIHYDROCODEINE–SCOPOLAMINE IN OBSTETRICS

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NEW narcotic agents for analgesia during labor are of some value to the obstetrician even if they do not materially reduce side effects, as long as depression of the fetal respiratory mechanism is not increased. More and more patients are becoming allergic to drugs such as morphine, meperidine (Demerol) and Dilaudid; therefore, the obstetrician cannot have too many such agents at his command. If a drug can be found which produces good analgesia with fewer side effects and less fetal depression, a real contribution can be made. Unfortunately, however, clinical evaluation of these factors is extremely difficult. Comparison with placebos is not clinically desirable, and even with their widespread use the drugs mentioned have few accurate standards for comparison. Also, the response of the individual patient to any one drug varies considerably.

This is a preliminary report on the use of dihydrocodeine* in first and second stage labor in 115 private obstetrical patients. The series is not large, having developed more slowly than anticipated mainly because of our belief that each patient should be individually evaluated with respect to the type as well as the amount of analgesia used. The conclusions reached, unfortunately, are based essentially upon clinical impressions.

Dihydrocodeine is closely related chemically to codeine, with a structural difference that the double bond in the ring carrying the hydroxyl radical is saturated by the addition of two atoms of hydrogen. The bitartrate salt is a white crystalline powder very soluble in water in contrast to the poorly soluble codeine sulfate. Such solutions are stable and may be autoclaved.

Dihydrocodeine has been used extensively since 1913 in Europe, Central and South America. Given subcutaneously it produces no local irritation. Beecher[1] reports that the subcutaneous dose of 30 mg. of dihydrocodeine per 70 kilograms of body weight is about as potent in analgesic properties as 10 mg. of morphine but of somewhat shorter duration of action. Keats and associates[3] found this dose only 9 per cent less effective than 10 mg. of morphine. In such a dosage it has been found to cause almost no demonstrable respiratory depression and a minimum of the other side effects of morphine such as nausea, constipation, and euphoria.

*The dihydrocodeine used in this series was Rapacodin furnished through the courtesy of Bilhuber-Knoll Corporation, Orange, N. J.

Thirty milligrams of dihydrocodeine has been found to exert an analgesic effect approximately equivalent to that of 65 mg. of meperidine hydrochloride. An increase in this dose causes some respiratory depression without much increase in the analgesic effect and is, therefore, not to be desired.

In this series, 30 mg. of dihydrocodeine and 0.4 mg. of scopolamine were initially used, followed by 0.4 mg. of scopolamine in 45 minutes. Medication was started with reference to pain as an indication rather than to any specific cervical dilatation. Scopolamine, 0.2 mg., was then used every one to 2 hours until delivery. The dihydrocodeine was repeated at approximately 4 hour intervals depending on the condition of the patient. During the early part of the series 8 patients were also given vinbarbital (Delvinal), 0.3 Gm. No attempt was made to restrict the use of dihydrocodeine just prior to delivery in order that the deleterious effect upon the baby, if any, might be detected.

Evaluation of the analgesia and amnesia must of necessity be considered together. The induction of good amnesia is somewhat aided by good analgesia. Scopolamine, used to produce the amnesia, is in part responsible for a patient's wildness in labor. However, if given to a person without pain stimuli, it causes peaceful sleep. Therefore, the analgesic evaluation of the dihydrocodeine is mainly based upon the degree of excitement shown by the patient.

TABLE I. FREQUENCY OF EXCITEMENT AND AMNESIA WITH DIHYDROCODEINE-SCOPOLAMINE IN LABOR

Excitement.—		
Wild	18	(16%)
Restless	23	(20%)
Quiet	74	(64%)
Amnesia.—		
Good	78	(68%)
Fair	30	(26%)
Poor	7	(6%)

Sixty-four per cent of these patients had almost no activity during a contraction and were completely quiet, resting well between; 20 per cent were restless, thrashing around with contractions, but these patients were essentially quiet between and easily manageable throughout; 16 per cent were wild and difficult to control, requiring side rails as well as forceable management.

Sixty-eight per cent of the patients questioned after delivery remembered nothing more than moving from the labor bed to the delivery table; 26 per cent remembered scattered events during their labor, while 6 per cent got little or no amnesic effect from the medications. The analgesic was administered to 2 per cent of the latter group such a short time before delivery that very little amnesic effect would be anticipated. Individual variation to the drug made it impossible to determine the interval between administration and response.

TABLE II. LENGTH OF LABOR

Less than 3 hours	34	(30%)
4 to 6 hours	36	(31%)
7 to 12 hours	39	(34%)
13 to 18 hours	6	(5%)

TABLE III. TYPE OF DELIVERY

Vertex, spontaneous	37	(32%)
Vertex, low forceps	70	(61%)
Vertex, midforceps	3	(3%)
Breech, forceps	5	(4%)

TABLE IV. ANESTHESIA

Cyclopropane	90	(78%)
Pudendal with Xylocaine	25	(22%)

As indicated in Tables II, III, and IV, most of the labors were under 13 hours with delivery effected by low forceps with cyclopropane anesthesia. Forty-four per cent of the patients were primigravidas.

TABLE V. CONDITION OF BABY

Spontaneous and immediate cry and respiration	111	(97%)
Slight delay of respiration	2	(2%)
Extensive resuscitation	1	(1%)
Stillbirth (2 weeks' duration)	1	

Only 3 babies had any delay in respiration. This was mild in 2, but one required resuscitation with an endotracheal catheter. It is interesting that in none of these 3 cases were there any complications of labor or delivery but that they all fell in the group of 8 patients who received vinbarbital. Each of these 3 received only one dose of dihydrocodeine with at least 2 hours between administration and delivery.

The only complication in the series was in a multiparous patient in whom highly irregular fetal heart tones were noted at 8 cm. dilatation. No cord could be palpated and when response to oxygen administration and Trendelenburg position failed to restore normal heart tones, delivery was effected through an incompletely dilated cervix. This baby not only showed no harmful delayed effects but respiration was immediate and spontaneous and no further cardiac irregularities were noted.

Summary and Conclusions

Dihydrocodeine may be added to the armamentarium of the obstetrician for use during labor. Its analgesic properties appear to be equivalent to those of 65 to 75 mg. of meperidine but with fewer side effects. Very little respiratory depression of the baby was found in this series.

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A GUIDE FOR IMPROVED TRANSVAGINAL PUDENDAL BLOCK

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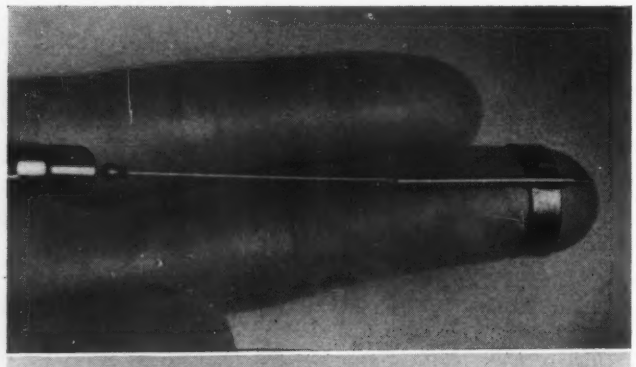
THE safety and efficacy of pudendal block have been demonstrated repeatedly in the literature. The transvaginal approach appears to be easier on the grounds of proximity to bony landmarks and the avoidance of lengthy passage through tissue spaces as in the transperineal approach. To control the tip of the needle and to prevent damage to vaginal mucosa and adjoining organs during insertion of the needle, a simple guide has been devised for use in the transvaginal technique.*

Fig. 1.



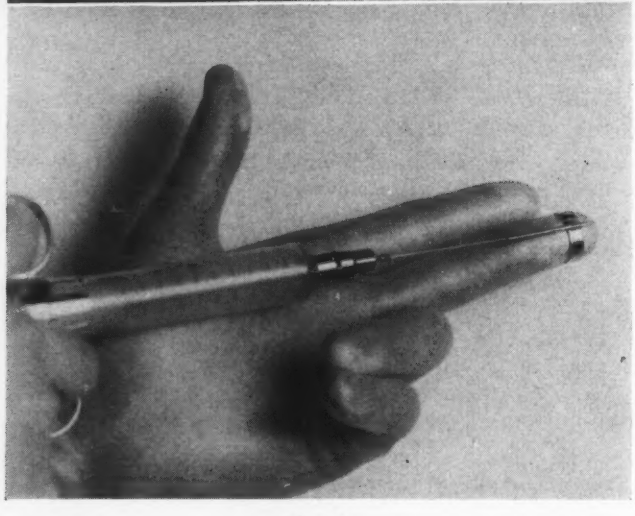


Fig. 2.

Fig. 1.—The pudendal needle is inserted in the carrier.
Fig. 2.—The syringe is palmed in the examining hand.

*Available through Fink Engineering Products, Box 2101, Lansing, Mich.

This guide consists of a malleable ring and an attached length of metal tubing or needle of suitable caliber, which acts as a carrier for the tip of the long pudendal needle. The ring is attached to the distal phalanx of the middle finger to be inserted into the vagina. The pudendal needle is inserted into the larger needle (carrier) attached to the ring, and the syringe is palmed in the examining hand (Figs. 1 and 2). The fingers are then inserted into the vagina until the ischial spine or sacrospinous ligament is palpated. The syringe and needle are then advanced through the carrier, giving pinpoint control to the site of the injection. This guide also permits use of a smaller gauge pudendal needle, minimizing tissue trauma and local pain.

1437 E. Michigan Ave.
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A NEW INSTRUMENT FOR LIGATION OF THE UMBILICAL CORD

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NUMEROUS devices for ligation of the umbilical cord have been used to produce hemostasis, ranging from cotton ties to metallic devices. Each has its own distinct disadvantages; the cotton ligatures will cut the cord if suddenly pulled too tightly, or the cord will bleed later if tied too loosely. Metallic devices likewise may cut or slip, and are more expensive than cotton ligatures. Recently, Dr. Ross B. Wilson of Lankenau Hospital devised a method using a narrow band of latex which, when spread and placed around the cord, provides continuous hemostasis and shrinkage of the dried cord stump. This has given excellent results at several Philadelphia hospitals. However, the metallic spreader used in applying the latex band provides only a two-way stretch which is too narrow an opening to thread the umbilical cord easily.

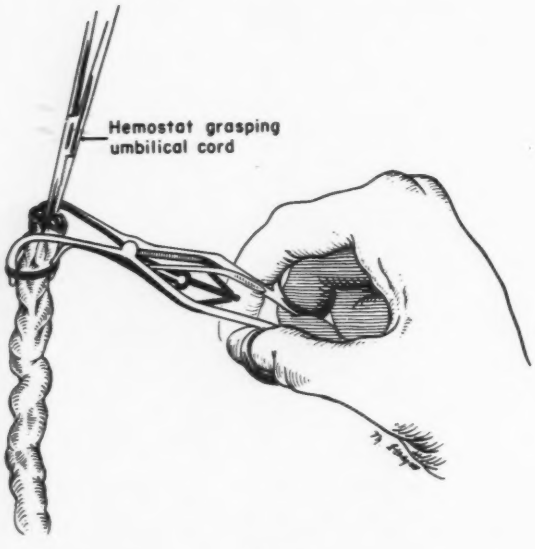

Fig. 1.

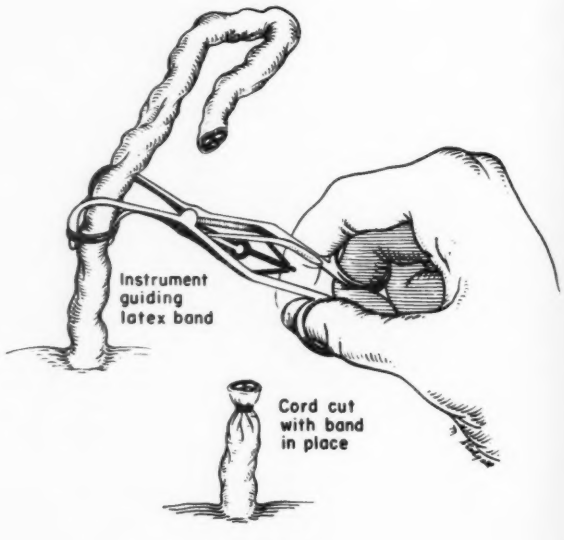

Fig. 2.

Fig. 1.—The three-pronged instrument opens the latex ligature so it will slip over the cord easily.

Fig. 2.—Ligature placed, cord cut.

The ligature carrier shown in the illustrations is a new instrument* which is so devised that it produces a triangular-shaped opening in the latex band. This is accomplished by placing a third blade to increase the spreading action of the instrument, making the opening sufficient to accommodate even the largest umbilical cords without difficulty.

*This instrument is made by George P. Pilling & Son, 3451 Walnut Street, Philadelphia, Pa.

The steps used in this method are as follows:

1. Place the small latex band on the instrument.
2. Spread the instrument with attached band, pass a hemostat through the triangular-shaped opening, and grasp the end of the cord (Fig. 1).
3. Pull the cord through the band, placing the latter approximately 3 cm. from the proximal end of the cord.
4. Release the band onto the cord and section the cord 2 cm. distal to the band (Fig. 2).

To obviate frequent sterilizations of the instrument, which are not necessary, the tip of the applier is kept in a solution of 1:1,000 aqueous benzalkonium chloride (Zephiran), as are the cut bands and hemostat. A small tray containing these materials is kept near the infant's crib adjacent to the delivery table.

The latex bands are 3 mm. in width and can be made at a cost of less than one-tenth of a cent per band. Long tubing may be purchased and cut into the small ligatures by the nurses preparing the delivery instruments. Once the instrument is purchased, the cost per delivery is minimal.

Summary

1. A new instrument is described which applies a latex band onto the umbilical cord for ligation.

2. Suggestions are made for its use.

Case Reports

BILATERAL TUBAL PREGNANCY

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BILATERAL tubal pregnancies, of the same age or of different ages, are considered the rarest form of double ovum twin pregnancies. Therefore an authentic case which meets the criteria as enumerated by Fishback[1] merits reporting. Fishback in 1939 pointed out that the embryo or chorionic villi must be present bilaterally in order to establish a diagnosis of bilateral tubal pregnancy.

The incidence of bilateral ectopic gestation at the Cook County Hospital, as reported by Abrams and Kanter[2] in 1948, was 1:1,580 ectopic pregnancies. Stewart,[3] in 1950, in his report of a case, reviewed the world literature and reported the incidence to be 1:725 ectopic pregnancies. In February, 1952, Hofmeister and Hultman[4] in their analysis of 83 cases of ectopic pregnancy at the Milwaukee Hospital listed a case of bilateral tubal pregnancy. In August, 1952, Evans and Goyanes[5] reported their case as the one hundred and forty-second authentic instance of bilateral tubal pregnancy.

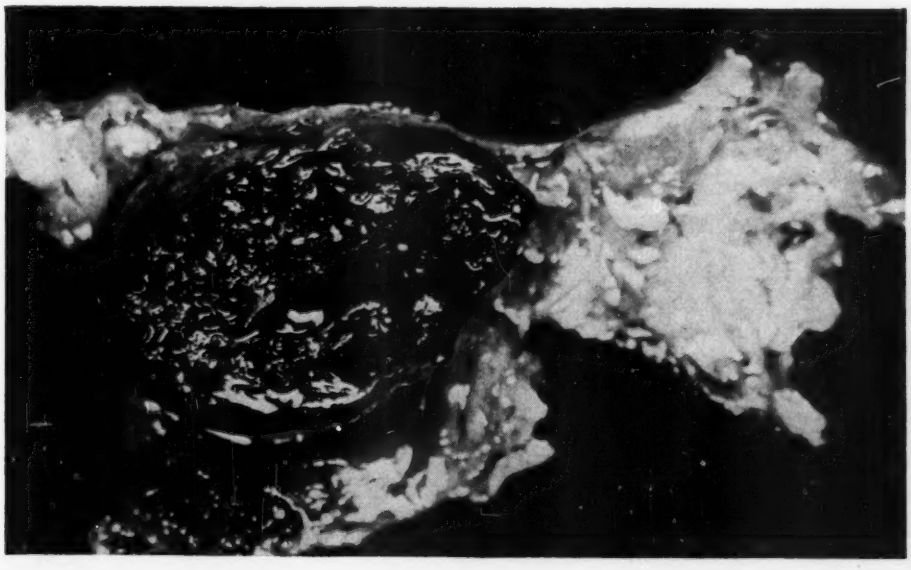
Case Report

V. A., a 27-year-old Negro woman, para iii, gravida iii, was admitted to the Gynecological Service of Provident Hospital on Feb. 7, 1954, complaining of generalized lower abdominal pain and irregular vaginal bleeding for the preceding month. Her last normal menstrual period was on Dec. 7, 1953. On Jan. 9, 1954, she started a regular menstrual period of 4 days' duration. Within several days she began to bleed irregularly and to have lower abdominal pain which was more marked on the right side. The pain and bleeding were increased on urination or defecation.

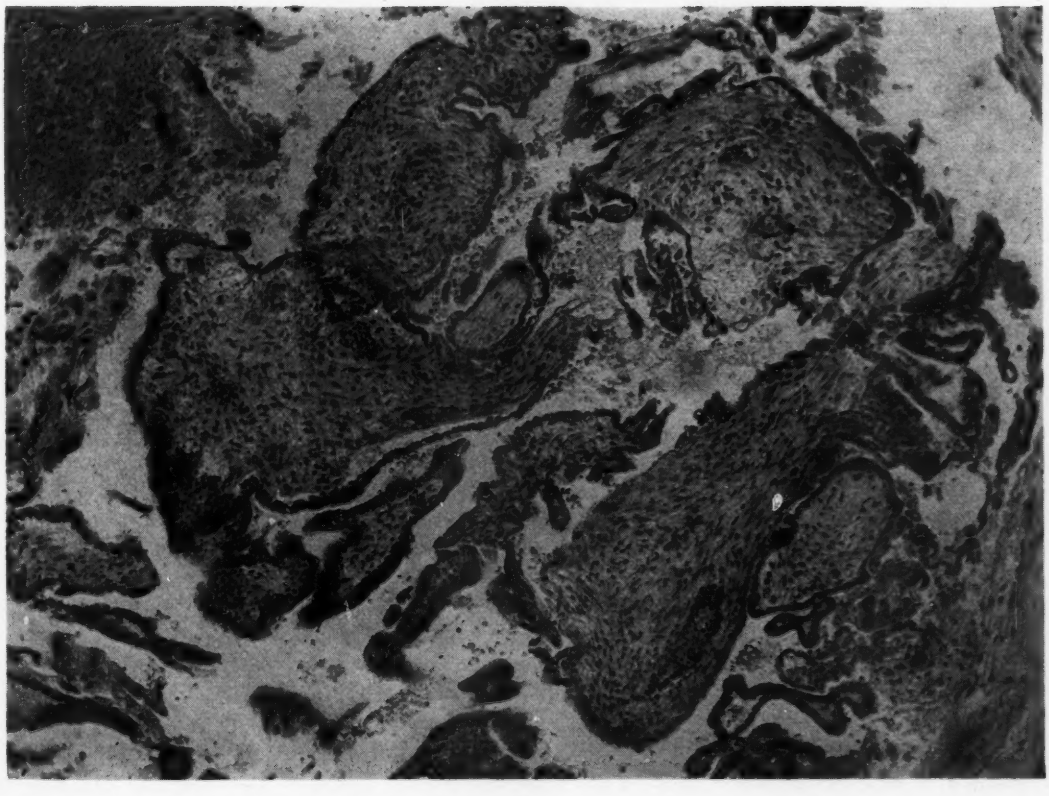
The past history disclosed the presence of pelvic inflammatory disease. The youngest child was 6 years of age.

The physical examination showed a well-developed, well-nourished woman in slight distress. The temperature, pulse, and respiration were normal. The blood pressure was 110/70. The abdomen was flat, soft, and nontender. On pelvic examination the cervix pointed down

and forward, and was freely movable with slight tenderness. The corpus was in first degree retroversion, firm, a little enlarged, with slight tenderness on movement. The right adnexa were thickened and tender. The left adnexa displayed no masses or tenderness. On speculum



A.



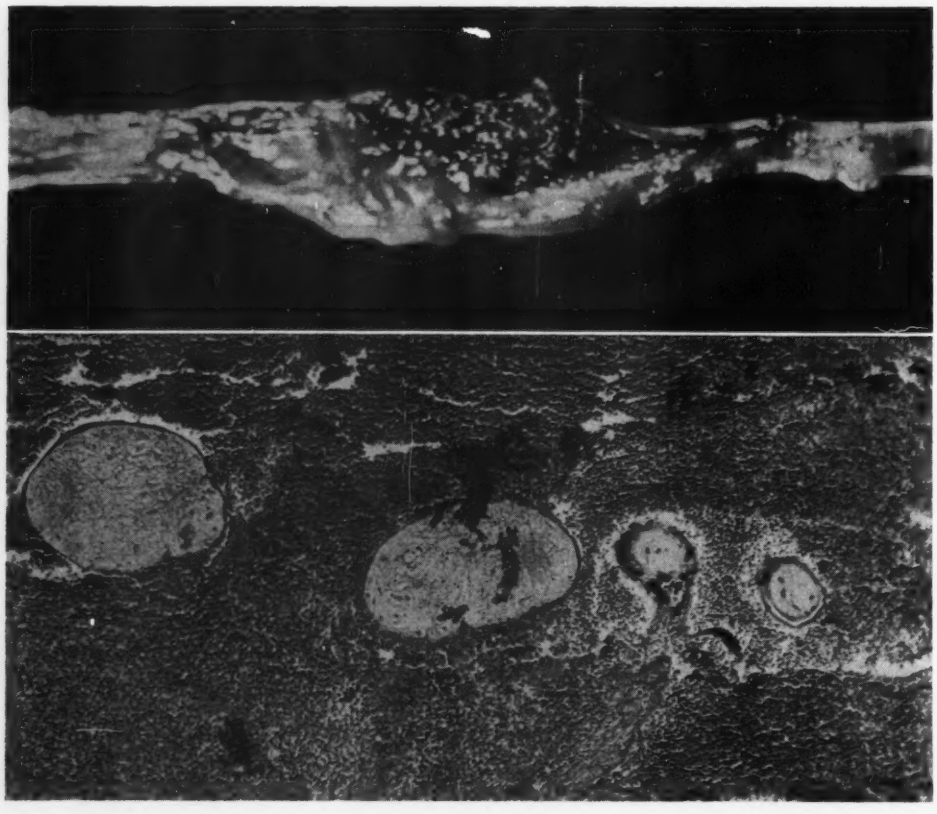
B.

Fig. 1.—*A*, Photograph of right tube showing rupture. *B*, Figure shows typical chorionic villi.

examination the cervix was eroded and the os was patulous. The following clinical diagnoses were entertained: (1) possible right tubal pregnancy, (2) subsiding pelvic inflammatory disease, (3) incomplete abortion.

Laboratory tests showed the following: hemoglobin, 13.3 Gm. per 100 c.c.; hematocrit, 43; white cell count, 14,200 with a differential of 80 per cent polymorphonuclear cells, 14 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophils, 2 per cent basophils. The sedimentation rate was 42 mm. per hour. Urinalysis was negative except that microscopic examination showed 10 to 12 white blood cells per high-power field. The sickling test was negative.

A.



B.

Fig. 2.—*A*, Photograph of left tube showing rupture. *B*, Figure shows typical chorionic villi.

An Aschheim-Zondek test was ordered and the patient was placed on antibiotic therapy. On Feb. 10, 1954, the Aschheim-Zondek test was reported positive. It was felt that the patient should have a vaginal examination under anesthesia, a curettage, a posterior colpotomy, or exploratory laparotomy. On examination the cervix was found to be patulous and readily admitted a small Hegar dilator. A moderate amount of decidual tissue was obtained on curettage. Colpocentesis was negative. The clinical impression at this time was that this was an incomplete abortion. The patient became asymptomatic and was discharged on the fourth postoperative day.

The patient was readmitted to the hospital one week later, on Feb. 17, 1954, because she had experienced an acute pain on the right side and had gone to the bathroom and had fainted. On admission the blood pressure was 90/60, pulse 120. She was immediately taken to the operating room. A pelvic examination was made and a markedly tender right adnexal mass

was found. A diagnosis of ruptured right tubal pregnancy was made and an immediate laparotomy was performed under general anesthesia. At operation a ruptured right tubal pregnancy was found. Since the right ovary was involved, a right salpingo-oophorectomy was performed. Before the abdomen was closed, a routine examination of the opposite tube was made and disclosed a hemorrhagic mass in the middle third of the left tube. A left salpingectomy was done. The patient received 1,000 c.c. of blood during the operation. Her recovery was uneventful and she was discharged on the ninth postoperative day.

Pathological Report (by Dr. N. I. Kohut).—

Right tube, right ovary, and fetus: Gross: The specimen consisted of a fetus which was 5 cm. in length, a torn ovary attached to a tube which was coiled so that it was 5 cm. in length and 3 cm. in width. There was a tear in the wall of the tube which contained blood clot and a soft gray friable placenta-like tissue. The ovary contained a large hemorrhagic corpus luteum, and the entire ovarian mass measured about 4 by 3 by 1 cm. (Fig. 1, *A*).

Microscopic: Portions of a corpus luteum of pregnancy were present in the ovary which also showed other developing Graafian follicles. A portion of Fallopian tube contained many well-preserved immature chorionic villi covered by two distinct layers of epithelium. The tube wall was edematous and had many dilated blood vessels, and at some levels showed trophoblastic invasion (Fig. 1, *B*).

Left tube: Gross: The specimen was a single Fallopian tube which measured 11 cm. in length. It had a diameter of 0.5 cm. for a distance of 3 cm., dilating to 1.5 cm. for a variable distance of 3 cm., and then 0.6 cm. for the next 3 cm. The serosal surface was gray and glistening and the fimbriated end was hyperemic with fibrous adhesions. Contained within the tube was a soft grayish-green tissue lying free except at the portion where the tube was most dilated, and here it was an adherent mass, dark red and yellowish tan, measuring about 1.5 cm. in greatest diameter. A section was taken of the tubal wall at the point of the adherent mass (Fig. 2, *A*).

Microscopic: This tubal tissue contained a poorly preserved, necrotic portion of placental tissue with ghosts of chorionic villi remaining, surrounded by organized blood clots and many pigment-filled macrophages. Portions of Fallopian tube wall were infiltrated by many inflammatory cells and partially surrounded the organized clot and old tissue (Fig. 2, *B*).

Diagnosis: Right tube—pregnancy of Fallopian tube; left tube—old pregnancy of Fallopian tube.

Comment

The pathological findings described fulfill Fishback's criteria. Since there are no characteristic signs or symptoms peculiar to this entity other than those referable to a unilateral ectopic gestation, this diagnosis is usually made at the time of operation. This case also demonstrates the importance of examining both adnexa in a laparotomy for an ectopic pregnancy.

Summary

1. A case of bilateral tubal pregnancy is presented.
2. The diagnosis of bilateral tubal pregnancy is made at operation.
3. Both adnexa should be thoroughly examined when a laparotomy is performed for unilateral tubal pregnancy or other adnexal pathology.

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A SUCCESSFUL PREGNANCY AFTER ENDOMETRIAL TUBERCULOSIS

A Case Report

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UNTIL very recently, the occurrence of an intrauterine pregnancy after proved endometrial tuberculosis has been open to question. Although there have been reports of such cases, authorities such as Stallworthy,[1] Cross,[2] and Halbrecht[3] have expressed their skepticism. Rabau,[4] Bromberg and Rozin,[5] and Halbrecht himself were finally able to report cases of cured endometrial tuberculosis in which pregnancy later occurred but ended in spontaneous abortion.

On the other hand, viable pregnancies after treated tubal tuberculosis have been reported. Up to 1953, 11 such cases had been found[6] and Halbrecht[3] has since added 2 more. The explanation for the better prognosis in tuberculous salpingitis as regards future pregnancy is that endometrial tuberculosis represents a more advanced stage of the disease. At this stage, even though the infection may be cured, the tubes will have suffered permanent and irreparable damage which precludes intrauterine implantation of the fertilized ovum.

Within the past year, however, 3 cases of successful pregnancy following treated endometrial tuberculosis have been reported in England.[7, 8] In the first case, the endometrium did not show evidence of tuberculosis histologically, but culture and guinea pig inoculation of the curettings were positive. Treatment with streptomycin and para-aminosalicylic acid was "erratic" and there were no further studies of the endometrium before pregnancy occurred. In the second case, endometrial tuberculosis was demonstrated histologically and a cure was proved by two negative curettings after treatment. In the third case, the diagnosis rested on culture of the curettings, the histologic examination and guinea pig inoculation being negative. After three months of treatment, the cultures were negative.

We wish to report another case of successful pregnancy which occurred after endometrial tuberculosis had been diagnosed and treated.

S. R., a 26-year-old Negro woman, para i, gravida i, was first seen in September, 1955, because of profuse vaginal bleeding when her expected period was ten days overdue.

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She thought she was having a miscarriage, a similar episode having occurred one year earlier.

The patient had had one normal delivery in 1951. The menarche was at the age of 13 and menses occurred every 25 days. Since her first pregnancy, she had been receiving intermittent treatment for pelvic "inflammation."

Physical examination showed no pelvic or other abnormalities. She was hospitalized and a curettage performed on Sept. 24, 1955. The curettings showed endometrial tuberculosis (Fig. 1). A chest x-ray and an intravenous pyelogram were normal.

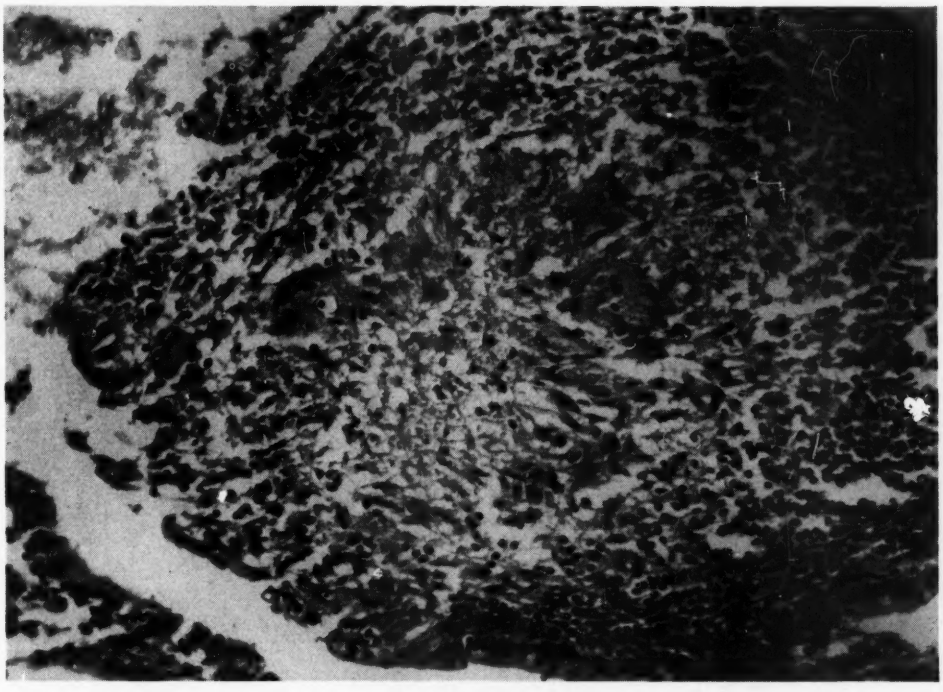

Fig. 1.—Photomicrograph showing the characteristic makeup of the tubercle, e.g., caseation, giant cells, epithelioid and small round cells. (×295; reduced ¼.)

On Oct. 7, 1955, treatment with Streptohydrazid* and PAS was started. The patient was given 10 Gm. of PAS and 1 vial of Streptohydrazid daily. The frequency of the injections was gradually reduced and treatment was finally discontinued in February, 1956, after 19 weeks. She received a total of 62 Gm. of streptomycin. Endometrial biopsies in November and December, 1955, were negative for tuberculosis. Normal menses were resumed in November. A hysterosalpingogram was planned in March, 1956, but she failed to menstruate that month and an Aschheim-Zondek test was reported positive.

The antepartum course was uneventful until Sept. 22, 1956, in the twenty.eighth week of gestation. At this time the membranes ruptured and a live male infant that weighed 3 pounds, 4 ounces was spontaneously delivered. There was excessive postpartum bleeding and a transfusion of 500 c.c. of blood was given. She also received 1.0 Gm. of streptomycin and 10 Gm. of PAS daily post partum. On the eighth postpartum day, a large fragment of placental tissue was passed and several days later a curettage was done for continued spotting. Examination of the placenta and curettings showed no evidence of tuberculosis and cultures and guinea pig inoculation of these tissues were also negative. The baby showed no signs of tuberculosis. He weighed 5 pounds, 2 ounces at the time of his discharge.

*Streptohydrazid is the trade name of Chas. Pfizer & Company, Inc. It contains 1.0 Gm. of streptomycin and 236 mg. of isonicotinic acid hydrazide per vial for injection.

TABLE I. CLINICAL AND LABORATORY DATA ON ALL CASES OF SUCCESSFUL PREGNANCY AFTER ENDOMETRIAL TUBERCULOSIS

	HALLUM AND THOMAS[7]	NORBURN AND WALKER[8]	NORBURN AND WALKER[8]	BOBROW, POSNER, AND FRIEDMAN
Number of previous pregnancies	One	None	One	One
Interval between last pregnancy and diagnosis of endometrial tuberculosis	One year	------	6 years	4 years
Antecedent history	Pulmonary tuberculosis after first pregnancy	"Congestion of lungs"	Pleural effusion and pneumonia	"Inflammation of stomach"
Presenting complaint at time of diagnosis	Dysmenorrhea, menometrorrhagia	2 year infertility	Menometrorrhagia for 3 years	Two episodes of irregular bleeding
Method of diagnosis	Culture and guinea pig inoculation	Histology	Culture	Histology
Length of treatment	7 weeks	?	13 weeks	19 weeks
Results of treatment	Not followed	Negative biopsy after 10 weeks; hysterosalpingogram showed patent right tube	Negative culture at end of treatment; both tubes patent by hysterosalpingography	Negative biopsy after 5 weeks
Interval betwen start of treatment and conception	6 weeks	28 months	12 months	5 months
Examination of placenta	Negative	?	Negative	Negative
Fetus	Normal	Normal	Normal	Normal
Postpartum course	Uneventful	Uneventful	Uneventful	Uneventful

Comment

We believe that this is a case of unequivocal endometrial tuberculosis which was cured and then followed by a successful pregnancy. Table I gives pertinent data on this and the 3 other cases previously reported.

The evidence for endometrial tuberculosis in the first reported case is incomplete. From our own[6, 9] and many other observations, we know the disastrous sequence of events that occurs when pregnancy and pelvic tuberculosis are present concurrently. The fact that the postpartum course in the first case was uneventful should mean that a cure had been effected. Yet we consider a complete cure of even minimal pelvic tuberculosis most unlikely after only 7 weeks of admittedly "erratic" treatment.

Is it possible that in the first as well as the third case, where histologic evidence was lacking, the patients had only tuberculous salpingitis, or, at the most, a beginning endometrial infection? When Halbrecht[3] receives a negative pathologic report from curettings and a positive culture from menstrual blood he believes the patient has only tuberculous salpingitis. On the other hand, English investigators[1, 10] consider positive cultures and guinea pig inoculations from endometrial curettings as positive evidence of endometrial tuberculosis, even when the histologic proof is lacking. Vollum[11] found that in 10 per cent of his cases of tuberculous endometritis the histologic examination was negative, whereas guinea pig inoculations were positive. Sutherland,[10] however, noted that, of 185 cases proved histologically, bacteriologic proof could be obtained only 141 times.

In our opinion, unquestioned histologic demonstration of a tuberculous lesion is the best proof of endometrial tuberculosis.

There is another explanation which could account for both the negative biopsies and the occurrence of normal pregnancies. All 4 cases may represent what has been termed "myometrial" tuberculosis.[12] This is an uncommon type which is not an extension of a tubal infection but is metastatic from a distant focus, usually the lungs, via the blood stream. There may be only isolated and widely scattered lesions in the myometrium. The endometrium overlying these foci may be involved too. It would be quite easy to miss these areas on curettage. Since the tubes are not involved in these cases, there should be no further bar to pregnancy after cure of the endometrial and myometrial lesions. The rarity of this type of pelvic tuberculosis approximates the rarity of intrauterine pregnancies after so-called endometrial tuberculosis.

In any event, it appears that some small hope for a successful pregnancy can be offered to the woman with minimal pelvic tuberculosis who receives early and adequate treatment. Should a pregnancy occur, it is advisable to give antituberculosis therapy ante partum and post partum.

Conclusions

1. A fourth case of successful pregnancy following a cure of endometrial tuberculosis is presented.

2. An explanation for the rarity of this fortunate happening is offered.

Addendum.—Since the manuscript was submitted for publication, another authenticated case of a successful pregnancy after treated endometrial tuberculosis has been found in the literature.[13] The patient was found to have endometrial tuberculosis after a curettage for an incomplete abortion. She was treated with PAS and became pregnant again 6 months

later. She had a normal full-term delivery of a live 7 pound, 7 ounce infant and her postpartum course was uneventful. Examination of the placenta and lochia for evidence of tuberculosis was negative. It is regretted that this report, actually the first such case recorded, escaped earlier notice.

We wish to thank Dr. Michael Cehelsky for supplying us with information for the case report, and Dr. George Hatzel for reviewing the pathologic material. We also wish to thank Mr. E. Entin for the photomicrograph.

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SUBCUTANEOUS EMPHYSEMA IN EARLY PREGNANCY

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SUBCUTANEOUS emphysema has been reported in numerous and various conditions, most frequently secondary to the same condition in the mediastinum. In reviewing the available literature, we find it reported often in pregnancy at the time of labor, but only twice associated with early pregnancy. The first case is that of Winans,[1] which is similar to ours. The second is that of Hovick and West.[2]

The following case is interesting because it was not associated with other demonstrable emphysema and the condition cleared although the apparent cause of it, pernicious vomiting, continued.

Case Report

Mrs. E. C., a 24-year-old gravida iii, para ii, was admitted to the gynecological service on Dec. 26, 1954, with the chief complaint of severe nausea and vomiting of one month's duration. Her last normal menstrual period was on Sept. 11, 1954. She had been to another hospital on November 11 and was thought to be normally pregnant at eight weeks. She was admitted on four occasions to this institution in the following month for intractable vomiting. She was also seen on numerous occasions in the accident room and at different times given Thorazine, Bonamine, and Dramamine. None of these drugs seemed to give her any relief. Severe acetonuria was always found except when she had received adequate intravenous fluids. During this period she had lost 24 pounds in weight. Blood studies, chest and skull x-rays, basal metabolism rate, and intravenous pyelography were within normal limits. On December 24 she left that hospital voluntarily and presented herself to us two days later.

On admission she appeared listless and apathetic but in no acute distress. Her lips were dry and cracked, but her skin was not markedly dehydrated. Pelvic examination showed a large, symmetrical, soft uterus, estimated at 14 weeks' gestation. Other significant findings were 1 plus albuminuria and 4 plus acetonuria. Diagnosis: Severe hyperemesis gravidarum and normal intrauterine pregnancy.

Hospital Course.—The patient was treated with intravenous fluids, dietetic measures, isolation, and psychotherapy, with progressive improvement. Her blood chemical studies showed low chlorides, potassium, and calcium, but were otherwise within normal limits. On physical examination, the neck appeared somewhat swollen, and definite crepitation could be elicited in the anterior neck and supraclavicular spaces. An x-ray on December 27 demonstrated the emphysema. There were no complaints of pain, pressure, difficulty in swallowing, or voice changes. The swelling subsided in a few days and the emphysema was no longer evident on palpation or x-ray on Jan. 3, 1955. All symptoms improved and the patient was discharged on the fourteenth day, only to be readmitted on January 12, for ten more days of therapy. There was no evident emphysema on this second admission. She was last seen in good condition on February 7, and was delivered of a normal female child without complications in June.

Comment

The rarity of subcutaneous emphysema in early pregnancy prompts us to report this case. Hovick and West[2] and Hamman[3] outlined conditions which may predispose to the development of mediastinal emphysema, together with the symptoms, physical signs, differential diagnosis, and treatment relating to it.

The present theory of penetration of air into the subcutaneous tissues is that, under violent retching or straining, or even without these phenomena, pulmonary alveoli are overdistended and air escapes through a direct rent into the adventitia of a blood vessel, into the lung parenchyma, and/or into the interstitial lung tissue. Thence, by tracts along the sheaths of the pulmonary vessels, air may work its way to the mediastinum and through loose connective tissue to the fascial planes of the neck. Another possibility of escape is through the aortic hiatus into the retroperitoneal space. Perforation of the trachea or esophagus could also cause this condition.

Summary

A case of subcutaneous emphysema in early pregnancy is presented. Only one similar case has been reported in the available literature. The pathogenesis has been briefly discussed.

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INTESTINAL OBSTRUCTION ASSOCIATED WITH A HIATUS IN THE BROAD LIGAMENT

A Case Report

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THERE are recorded in the literature only 43 cases of intestinal obstruction caused by the herniation of a loop of ileum through a hiatus in the broad ligament. In addition, there are reports of 4 other cases in which a hiatus occurred without herniation or the complication of strangulation obstruction. Another case has also been described in which an ovary herniated through a defect in the broad ligament, producing signs and symptoms of an acute abdominal crisis, making 48 reported cases of hiatus in the broad ligament. Our case, described herein, is the forty-ninth.

The earliest description of strangulation through defects in the broad ligament was given in 1861 by Quain[13] who found the condition at autopsy. Forty-nine years later Barnard[3] described a specimen from the Museum of the London Hospital. Thereafter, reports were frequent, the greatest number occurring between 1920 and 1940.

In a comparatively recent review Baron[4] stated that in 17 of 40 recorded cases of intestinal strangulation the patients had previously undergone uterine suspensions of the Baldy-Webster type. In this type of uterine suspension the essential steps are (1) to pass the round ligaments through perforations made in the broad ligaments, and (2) to imbricate them with sutures to the posterior surface of the fundus of the uterus. He also noted that in these same 40 cases one half of the defects involved both layers of the broad ligaments; in only 5 were there definite hernial sacs composed of peritoneum.

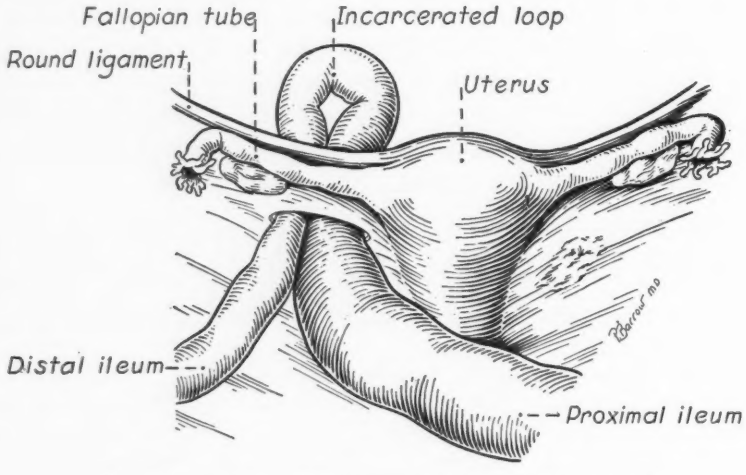
In his discussion of etiology, Baron considered uterine suspension as the most frequent predisposing condition. With the exception of 4 patients, all were parous nonpregnant women. It is of interest that one patient with intermittent episodes of abdominal pain, nausea, and vomiting remained free from recurrent attacks only during her pregnancies. All ages, from 18 to 79 years, were represented, the average age being approximately 44 years. Only 2 patients presented any evidence of pelvic inflammatory disease, and in only 2 were the defects bilateral.

Goode and Newbern[10] reported 17 cases of broad ligament defects which were not associated with uterine suspensions. Sixteen of these occurred in the mesosalpinx. This is a relatively avascular area, and it is possible that such defects represent embryological malformations.

In 1930, Caplan[6] reported an intestinal obstruction through such a hiatus in a patient who had undergone a laparotomy three years prior to the obstruction. No defect had been found at the earlier operation.

In the Italian literature, Amadei[1] reported a case in which he suspected the diagnosis of intestinal obstruction secondary to a herniation of bowel through the broad ligament. This patient had undergone a uterine suspension three years previously. This is the only case in which the diagnosis was made prior to a laparotomy.

Since Baron's summary of 46 cases, 2 others have been reported. One[15] of these patients was a 67-year-old multipara with a history of nausea and vomiting for a period of twelve hours prior to admission. She continued to have bowel movements, and during a period of observation her pain was localized in the right lower quadrant. With a provisional diagnosis of acute appendicitis, a laparotomy was performed. There was in the right ligament a 4 cm. defect through which a loop of small intestine passed. The proximal portion of the loop was distended, and the distal portion was collapsed. There was no definite hernial sac. The defect was between the uteroovarian ligament and the Fallopian tube which were divided, thereby dividing the constricting ring. Recovery was uneventful.



Incarceration of ileum in broad ligament, as seen from above.

Fig. 1.

The second patient[7] was a 38-year-old woman who six years earlier had undergone a uterine suspension by the Doléris technique. Three years after the suspension the patient noted the onset of cramping abdominal pains, nausea, and vomiting which recurred intermittently over the period of the ensuing years. On admission the patient presented no roentgenological evidence of intestinal obstruction, but at laparotomy a loop of small bowel was found in a defect in the broad ligament.

Although treatment has varied from resection of the structures forming the ring to simple closure of the defect, there have been no reported recurrences.

Case Report

L. M., a 60-year-old white woman, was admitted to Grady Memorial Hospital on Aug. 26, 1955. After breakfast, two days prior to admission, the patient noted a gradual onset of left lower quadrant abdominal pain which increased in intensity and became generalized over the abdomen. Three hours following the onset the patient began to

have persistent nausea and vomiting. She was unable to retain any food or liquids for the subsequent two days. On the morning the pain began the patient had one bowel movement. Thereafter she was unable to have bowel movements, although she took enemas and laxatives.

Ten years before the present admission to the hospital, she had undergone uteropexy, prior to which she had had a nephropexy and a choledochoduodenostomy. These procedures were performed in another city, and the details could not be obtained.

Physical examination showed a well-developed and well-nourished white woman who was in acute distress from severe cramping lower abdominal pain, nausea, and vomiting. The vital signs were as follows: blood pressure 112/80, pulse 102, respirations 23, and temperature 100.6° F. Her breath had a feculent odor. The abdomen was not distended and was soft to palpation. No rebound tenderness was elicited. Peristalsis was hypoactive, but high pitched. No mass was palpable, nor was there any rectal or pelvic mass, but there was tenderness to deep palpation. Films of the abdomen disclosed multiple dilated loops of small bowel. She had acetonuria, and the hemoglobin was 11.75 Gm. per cent. A Miller-Abbott tube was inserted and antibiotics were administered. When the fluid and electrolyte balance was adequate, a laparotomy was performed.

The peritoneal cavity was filled with dilated, dusky loops of small bowel. There was approximately 400 c.c. of pink peritoneal fluid. The dilated bowel was traced distally and a loop of distal ileum was seen to pass through a 3 cm. defect in the left broad ligament. This loop was freed by dividing the left round ligament and the Fallopian tube. The transected ends were then reperitonized by invagination. The right broad ligament was intact, but scarred, and there were many small pockets or its surface (Fig. 1). The exact type of suspension procedure which had been used ten years earlier was not obvious, but it appeared that the broad ligaments had been used to support the uterus.

The patient's postoperative course was uneventful, and she was discharged from the hospital on the eighth day after operation. When last seen three months following her discharge, she was asymptomatic with the exception of mild urinary frequency and dysuria.

Summary

1. Hiatus of the broad ligament can be classified as congenital or acquired.

2. In the congenital variety the defect is usually in an avascular area in the mesosalpinx.

3. Previously performed uterine suspension, especially of the Baldy-Webster type, is the most frequent cause of the acquired variety. Nineteen such cases have been reported.

4. In 44 of the 49 reported cases, the presenting symptoms were those of intestinal obstruction.

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INJURIES TO THE BOWEL AS THE RESULT OF AN ENEMA

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IT IS not generally recognized that the rectum and sigmoid colon may sustain serious injury as the result of an improperly administered enema.

Ordinary sensation in the rectum ends at the dentate margin; proximal to that point the innervation is automatic (sympathetic), and considerable mutilation of the rectal wall may take place without the patient experiencing discomfort.

Enemas may cause minor abrasions and tears in the mucosa. These minor injuries heal without difficulty.

Physicians generally do not recognize how little pressure is required to rupture the colon or rectum.

Burt's[1] experiments performed at autopsy upon the alimentary tract of 18 human beings showed that the average pressure required to perforate the intestine was 4.07 pounds per square inch (21 cm. mercury). The highest pressure supported by a segment of adult intestine was 8.4 pounds per square inch (43 cm. mercury). Introduction of air twice as fast lowered the pressure required for perforation.

Although Burt found the sigmoid to be the second strongest segment of the alimentary tract which he tested, it is the most commonly ruptured in clinical experience, particularly in injuries from compressed air, and in other injuries resulting from suddenly increased intraluminal pressures of the bowel.[4-8]

Wangensteen[2] says that when pressure is introduced into the alimentary tract the greatest stress is borne by the intestine with the largest diameter; that is, the tension on the wall of the intestine increases in proportion to the diameter of the viscus. This phenomenon probably accounts for the rupture of the larger segments of the alimentary tract, e.g., stomach and cecum, at lower intraluminal pressures than segments of smaller diameter.

Two types of patients seem to be particularly vulnerable to perforation by enema: the patient over 55 years of age, and the pregnant woman at term.[9, 10]

One of the essential factors in producing the injury is the use of a hard nozzle, usually of bone, hard rubber, or metal, and several inches in length.

Since such nozzles are usually attached to syringes or rubber bulbs, the pressure with which the enema is given becomes the second important consideration. Such pressures may result from common error of using a long rectal tube and holding the enema can or bag high in the air. Third, perforation is most likely to occur with the patient in the sitting posture.

Pratt and Jackman[11] have suggested that enema nozzles should always be fitted with a flange large enough to prevent their being inserted for more than two inches.

When perforation occurs the patient may rarely experience sudden severe low abdominal pain.

Because of the relative absence of pain and the importance of early diagnosis, Pratt and Jackman are convinced of the value of proctosigmoidoscopic examination as soon as there is reason to suspect rectal injury. When the site of the perforation is seen, a catheter is passed into the hole and left there to guide the surgeon at laparotomy. Operation consists of identifying the hole in the bowel and repairing the defect.

Thirty cases of actual perforation have been reported in the literature, and to them we add another.

Case Report

D. W., a Negro woman aged 35, was admitted to the Georgia Infirmary on Jan. 19, 1956. She complained of vaginal bleeding for the past 12 weeks. She had had a bilateral salpingo-oophorectomy and appendectomy on March 12, 1955, for chronic pelvic inflammatory disease. In October, 1955, she began to have uterine bleeding. A dilatation and curettage was done in November, 1955. The patient received 7 pints of blood because of severe secondary anemia. She continued to bleed and at this admission the hemoglobin was 37 per cent. After the intravenous administration of 1,500 c.c. of blood a total hysterectomy was performed on Jan. 24, 1956.

On the fifth postoperative day, the patient was given a soapsuds enema at 11 A.M., with good results. At 12:05 P.M. she complained of lower abdominal pain, and vomited. The patient passed a large amount of flatus at 2:30 P.M. and afterward said she felt much better. At 4 P.M. she again complained of abdominal pain. At 9 P.M., according to the nurse's notes, she continued to be restless, had a cold sweat over her face, and seemed to be in much pain. The nurse did not notify any physician. The next morning the patient had abdominal distention and signs of a generalized peritonitis. The patient volunteered the information that the enema yesterday "almost killed her." In consultation it was decided to treat her with antibiotics and general supportive therapy.

The patient responded well to this regime and had a spontaneous bowel movement on the ninth postoperative day. On the tenth postoperative day, the Wangensteen drainage was discontinued.

The patient had a soft yellow stool on the twelfth postoperative day. Her temperature began to rise again, she had chest pain, and her condition began to deteriorate. The abdomen became more distended, despite reinstitution of the Wangensteen drainage, and peristalsis disappeared. She developed pain in the left chest, signs and symptoms of pleurisy, and purulent sputum. X-ray examination showed atelectasis and pneumonia in both lower lobes. She was bronchoscoped on the eighteenth postoperative day because of suspected lung abscess. No lung abscess was found. She grew progressively worse. The nonprotein nitrogen rose to 61.1 mg., and the urinary output dropped to 200 c.c. daily. She died on Feb. 12, 1956, at 6:40 A.M., the nineteenth postoperative day.

The clinical impression at the time of death was generalized peritonitis, subdiaphragmatic abscess on the left, lung abscess, left. Autopsy revealed 2,000 c.c. of purulent material under the left diaphragm, without perforation into the left pleural cavity. Other similar areas of purulent exudate were present in the left abdominal gutter. They were separated into loculated areas of varying size. They were all filled with various amounts of similar partially coagulated exudate and were actually small abscesses. The colon was traced from the rectum upward, across the pelvic brim. At the pelvic brim it adhered to the adjacent peritoneum and was covered by adherent small bowel and omentum. The omentum was slowly stripped away, as was the adherent small bowel, and a 2 cm. tear was found in the anterior portion of the colon as it passed over the pelvic brim. An area of purulent material beneath this tear extended downward onto the psoas muscle. The entire intestinal tract within the abdominal cavity was extremely friable, edematous, and inflamed at all levels. All the bowel loops adhered to each other and were covered with similar greenish-yellow exduate.

The internal genital organs were absent. The area of the recent surgical operation showed the pelvic floor to be covered entirely by peritoneum. No areas of blood clot or suppuration were found beneath it.

The rest of the organs were not remarkable except for marked atelectasis of both lower lobes of the lungs, which was confirmed by microscopic examination.

A microscopic examination of sections of small intestine and of colon from the area of perforation showed them to be covered by a very thick layer of acute inflammatory exudate which showed areas of organization.

The anatomical diagnosis was perforation of the colon with peritonitis, and acute, massive atelectasis of both lower lobes.

Comment

Minor abrasions of the rectum probably are fairly common following the administration of enemas.

Intra-abdominal perforation of the rectum or sigmoid is a relatively rare condition. Only about 30 previous cases have been reported in the literature.

Most such accidents would be avoided if patients, nurses, nurses' aids, and orderlies were instructed more fully than at present in the proper way an enema should be given. Especially should it be emphasized that, once the enema nozzle has been inserted past the sphincter, it need not be inserted further. Large rectal tubes should not be inserted into the rectum. The patient should be cautioned to avoid sneezing, coughing, sudden movements, or straining while the enema tip is in place.

Perhaps replacing the old style enema with commercially prepared enemas in plastic bottles with short tips would reduce the incidence of these distressing accidents, as no reports mention these agents as causative factors of rectal perforations.

Summary

1. A case of traumatic perforation of an apparently nonpathologic sigmoid with a postoperative enema is presented.

2. The signs and symptoms following traumatic colonic perforation and the anatomic, physiologic, and pathologic factors are enumerated.

3. The literature of traumatic perforation of the colon is reviewed.

4. A suggestion is made that might prevent these accidents.

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RUPTURED ENTEROCELE

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ALTHOUGH the development of an enterocele is not an unusual complication following vaginal hysterectomy for prolapse, the delayed rupture of an enterocele with subsequent evisceration has been recorded in the literature but three times.[1, 3, 5] A case of this type has recently been treated by us and, because of its rarity, is being reported in detail.

Report of Case

The patient, a 66-year-old woman, para ii, gravida ii, registered at the Mayo Clinic June 13, 1953, requesting advice regarding recurrent pelvic relaxation.

Her past operative history consisted of uterine suspension and appendectomy in 1923, vaginal hysterectomy and plastic repair in 1950, and a vaginal plastic operation in 1952. Little information could be obtained regarding the exact nature of these operations, which had been performed elsewhere. A mass had been noted protruding from the vagina less than 4 months after each vaginal procedure.

When we were consulted 7 months after the last operation, the patient stated that the vaginal prolapse was increasing rapidly in size. There was no history of dysuria or stress incontinence of urine. Additional complaints consisted of loss of weight, chronic fatigue, and constant thirst.

The results of general physical examination were essentially normal except for the findings on pelvic examination. Her height was 5 feet, 7 inches; weight 143 pounds (normal 155); blood pressure 160/80, pulse 70, and temperature 98.6° F. There was complete prolapse of the vagina through the introitus, apparently the result of a large enterocele. The base of the bladder and urethra appeared to be well supported and there was an adequate perineal body.

Laboratory tests revealed a hemoglobin of 12.7 Gm. per 100 c.c. of blood; blood group A, Rh negative; urine—specific gravity 1.016, albumin negative, sugar Grade 4, acetone negative; and blood sugar 277 mg. per 100 c.c. Medical consultation was obtained, and the mild diabetes mellitus was regulated by means of diet and insulin therapy.

Vaginal repair of the Grade 4 (on the basis of 1 to 4) enterocele was advised. It was emphasized that the process of repair would diminish the depth of the vagina substantially, but this caused the patient little concern.

Operation was performed June 27, 1953. The large enterocele sac was opened and dissected free from the rectum and bladder. Several interrupted sutures were inserted to approximate the uterosacral ligaments in the midline anterior to the rectum. After excision of redundant peritoneum, a purse-string suture was placed as high as possible, closing the peritoneal defect. The rectovaginal fascia, which appeared unusually attenuated, was approximated anterior to the rectum with interrupted sutures, the excess vaginal mucosa was removed, and the incision was closed with interrupted sutures of No. 1 chromic

*The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

catgut, the material used throughout the operative procedure. A well-supported vagina of 6 cm. depth resulted. An iodoform pack was placed in the vagina and a retention catheter in the bladder.

These were removed on the third and fourth postoperative days, respectively. The highest temperature elevation to 100° F. occurred on the second postoperative day. The patient was dismissed from the hospital on the ninth day, and returned to her family physician for subsequent care on the seventeenth postoperative day. At this time, examination disclosed the suture line well healed, the vaginal vault well supported, and the vagina shortened about 60 per cent. She was advised to abstain from strenuous activity for 3 months and to return for evaluation at the end of this period.

The patient was next seen May 9, 1954, at 7:45 P.M., in the emergency room of St. Mary's Hospital. She stated that vaginal prolapse had recurred about 4 months after operation but had caused little distress. Normal activity without utilization of any vaginal support had been continued until 10:00 A.M. on the day of admission. At this time a severe sharp pain developed in the right upper quadrant of the abdomen, which extended to the right supraclavicular area, the right shoulder, and down the arm. Soon thereafter the patient noted a sanguineous vaginal discharge followed by the appearance of a purple mass at the vaginal introitus. When she consulted her family physician, she was referred promptly to the hospital via ambulance.

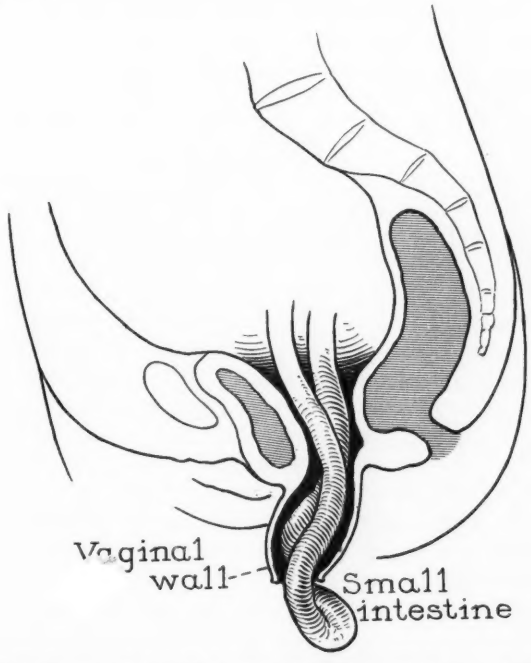

Fig. 1.—Prolapse of small bowel through rent in everted vagina.

The vaginal introitus was obscured by protrusion of a loop of small bowel about 2 feet in length (Fig. 1). During the time necessary to prepare the patient for operation, medical consultation was obtained regarding the diabetes.

After thorough preparation of the abdominoperineal area, cleansing of the intestine with saline solution, and administration of spinal anesthesia, the loop of small intestine, which appeared to be of good color, was returned to the abdominal cavity with some difficulty. There was a large defect in the posterior vaginal wall near the vault, presumably in the area of previous repair of enterocele. The peritoneum was closed with a purse-string suture. The redundant vaginal mucosa, which appeared to be the site of a

decubitus ulcer, was excised and the defect was closed with interrupted sutures of No. 1 chromic catgut. An iodoform pack was placed in the vagina and a retention catheter in the bladder.

Penicillin and dihydrostreptomycin were administered twice daily. The highest temperature recorded (99° F.) occurred on the third postoperative day. Convalescence was uneventful, and the patient was dismissed from the hospital on the tenth day.

When examined 2 months after operation, the vagina appeared to be well supported, although shortened approximately 60 per cent; however, the enterocele recurred again 4 months later. Initially, the use of a Tampax sufficed to control symptoms but more recently a No. 2 ball pessary has been necessary to support the vagina. The patient understandably is reluctant to undergo additional surgical treatment as long as she remains comfortable with this management.

Comment

Three cases of protrusion of a loop of bowel through a ruptured enterocele sac have been previously reported in the literature.

In the case reported by Bröse[1] in 1909 the patient had a history of three operations for vaginal prolapse over a 20 year period, the last of which had consisted of total hysterectomy with removal of the upper part of the vagina. An enterocele with a decubital ulceration of the overlying vaginal mucosa subsequently developed. More than a year after the hysterectomy the enterocele ruptured at the time of defecation, allowing a loop of bowel to protrude and become strangulated. At operation the vaginal opening was enlarged, the bowel was replaced, and the vagina was extirpated, after which the levator muscles and the vulva were united, forming a "perineum" from the anus to the urethra.

Rieunau[5] reported a similar case in 1933. In this instance an enterocele had developed after vaginal hysterectomy for uterine prolapse. Rupture of the enterocele with vaginal evisceration occurred 14 years after the hysterectomy. The prolapsed bowel was reduced after the abdomen had been opened through a lower midline incision, and the perforation was closed in two layers.

In 1949 Fox[3] reported the case of a 74-year-old woman, para ii, on whom vaginal hysterectomy had been performed by the Mayo-Ward technique. The upper portions of the broad ligaments were interposed between the symphysis pubis and the bladder. The posterior vaginal opening was closed by means of a Ward rectopexy suture. At operation the rectovaginal fascia appeared unusually thin. When the patient was examined 6 weeks later, a small enterocele was noted high in the shortened vagina. Fifteen months after operation, while she was at the toilet, several loops of ileum protruded. At operation the finger-tip opening in the posterior vagina was enlarged, the intestine was replaced, and the peritoneum was closed. The dissection was carried laterally and repaired routinely. A 3 month follow-up did not disclose any evidence of recurrent enterocele.

There have been other reports in the literature of prolapse of various organs through the vaginal vault, but uniformly they have been in the immediate postoperative period.

Cullen[2] mentioned a patient of Kelly's who died from peritonitis after vaginal hysterectomy because a loose vaginal pack allowed a knuckle of intestine to prolapse. Reference was made by Cullen to similar cases reported by Reichel and by Bokelmann, Leopold, and Landau. There are in addition many isolated reports of bowel, omentum, or ovary appearing in the vagina soon after an operation. Symmonds, Counseller, and Pratt[6] have reported 3 cases and collected from the literature 17 instances of prolapse of the fimbriated extremity of the Fallopian tube into the vagina. Theoretically this latter

situation could provide a defect of the vaginal vault through which a delayed prolapse of intestine could occur. However, in each of the 4 cases of vaginal evisceration recorded, the rupture of an enterocele has been considered the causative factor.

The impressive feature of the 3 cases reported in the literature, as well as of the present case, is that each patient had undergone single or multiple vaginal operations previously. It must be assumed either that an enterocele was overlooked at the time of these operations or that the tissues available for repair of the defect were so attenuated that the enterocele promptly recurred and subsequently ruptured. It is surprising that rupture of an enterocele with evisceration is not encountered more frequently, since the scarred, avascular, and atrophic vaginal mucosa covering the enterocele, abetted by decubitus ulceration, provides little support for the hernia.

In retrospect, it is apparent that the patient reported upon here would have benefited by total vaginectomy with levator and vulvar approximation initially rather than repair of the enterocele with preservation of the vaginal canal. Vaginectomy was not considered at the time of repair of the evisceration, since the condition of the patient did not justify prolonging the operation. In view of the fact that this patient is not particularly interested in the preservation of vaginal function, total vaginectomy will be the procedure of choice if she is operated on again.

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Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

Diseases of the Breast. By C. D. Haagensen. 751 pages, 404 figures. Philadelphia, 1956, W. B. Saunders Company. $16.00.

Dr. Haagensen has devoted his professional life to the treatment of diseases of the breast and to cancer of the breast in particular. The book reflects the thoughtful character of his approach to cancer and his precise and orderly study of the problem. There is a wealth of statistical detail which is clearly and simply explained in the text and the book is extensively illustrated by reproductions of the highest order of clarity.

Necessarily any book as careful and honest as this one suffers from the disadvantages inherent in writing about cancer of the breast so long as its etiology is unknown and its proper treatment not established. It was perhaps fortunate for Halsted that he enunciated his principles of the ideal cancer operation with respect to cancer in the mammary gland, a skin appendage to which, or at least so it was thought for a long time, his tenets were particularly applicable. The recent re-emphasis on the internal mammary pathways and supraclavicular metastasis is a new reminder of the essential puerility of the operative attack on cancer. It is based on the presumption that up to a given time in all cancers it is possible to establish a cure by a local operation. This concept is sound enough although as Haagensen shows it applied to only a very limited number of cases of breast tumor, or for that matter, of any other tumor by the time it is recognizable. Too many surgeons have lost sight of the fundamental basis for cancer operations and have "extended" operations far beyond the bounds of reason. In considering the operation for carcinoma of the breast, Haagensen is a Halstedian purist. He is almost vitriolic in disparaging the "standard American radical mastectomy with its minimal skin excision and thick skin flaps." It distresses him, therefore, to be unable to find statistically in his own hospital, or in any other published series, that wide skin excision and skin grafting are incontrovertibly superior to the more limited procedure. Quite soundly he indicates the probability that in many hospitals skin grafts are reserved for only the advanced cases, and that in any case the patient with grafts heals more rapidly and is less likely to have infection, and discomfort from tension.

In the early chapters on diagnosis and the natural history of the various types of breast tumors, there are numerous clearly expressed attitudes of such soundness and importance that it would be worth while collecting them into a small pamphlet for medical students and general practitioners. "It is never safe to perform radical mastectomy without microscopic proof of the nature of the lesion'' is perhaps the most important.

Haagensen's opinions on any form of breast disease are of interest. He dislikes aspiration as likely to be misleading. As between excisional biopsy and incisional biopsy he makes a good case for the small incisional biopsy which cuts through tumor-bearing lymphatics only on its way to the tumor and not on all sides of it as in the excisional biopsy. He does not favor prophylactic castration. There is a nice discussion of the relation of cystic disease to cancer of the breast, with a study of the statistics from various sources analyzed in different manners. While in this chapter no hard and firm conclusion appears to be arrived at, on page 720 Haagensen makes the flat statement that cancer is four times as frequent in women who develop grossly evident breast cysts. There is a good discussion of that troublesome lesion, intraductile papilloma, with the wise warning to avoid reliance on frozen sections. Dr. Haagensen and Dr. Stout, whose pathologic studies are the basis for much of the work, do grade breast cancers and feel that the grading is more informative prognostically than the histologic type.

The storm which arose some years ago when Haagensen described carcinoma during pregnancy as being categorically inoperable has made him a little more cautious on this point. Haagensen's whole thesis of the treatment of cancer of the breast is that early cases can be cured by the meticulous Halsted operation, and that more advanced cases cannot be cured by any operation and the patients' lives will actually be shortened by operation. At present he is engaged in the experimental program of triple biopsy—biopsy of the gland at the apex of the axilla, biopsy of the breast, and biopsy of the internal mammary nodes in the upper three interspaces. Radical mastectomy is then performed only in the patients in whom the regional lymph node biopsies failed to reveal metastasis.

Discussions of hormone and roentgen therapy of carcinoma of the breasts are not as detailed as the surgical sections.

A book of this kind can leave one more depressed than ever over the prospect of treating cancer by surgical resection. Fundamentally, that is probably the sound reaction from the long-term viewpoint. From the immediate viewpoint the statistical and historical review gives sharp evidence that inadequate operations cure few patients and that the well-performed radical operation performed in time gives an incidence of 80 per cent 5 year clinical cures in Haagensen's personal series of patients without involvement of the axillary nodes and of 40 per cent in patients with involvement of the axillary nodes.

Finally, the stand is taken that carcinoma of the breast in women of all age groups in good enough general condition to withstand operation should be treated by radical mastectomy except in the presence of: (1) extensive edematous skin over the breast; (2) satellite nodules in the skin over the breast; (3) inflammatory carcinoma; (4) parasternal tumor nodules; (5) proved supraclavicular metastases; (6) edema of the arm; (7) distant metastases.

Any two of the following grave signs with local disease are also contraindications: ulceration of the skin, edema of the skin of limited extent, solid fixation of the tumor to the chest wall, axillary lymph nodes more than 2½ cm. in diameter, and fixation of the axillary lymph nodes to the skin and deep structures.

Table 106 is particularly devastating. It lists the results at the Presbyterian Hospital of radical mastectomy in what in retrospect, by the above criteria, were considered to be categorically inoperable groups of cases. There were no 5 year clinical cures. This of course is not to state that the lives of these patients were necessarily shortened by operation, nor that they were not prolonged.

Photokolposkopie und Photodouglasskopie. By Dr. Friedrich Menken. 58 pages and 90 illustrations. Wuppertal-Elberfeld, 1955, W. Girardet.

A short monograph details the indications and technique of colpophotography and photoculdoscopy. The first section of the work deals with general matters relating to the

development of carcinoma and its early detection. The second section enumerates the details, techniques, and indications for the application of photography to the already established techniques of culdoscopy and colposcopy.

The final section of this volume consists of a large number of illustrations, most of which are colored pictures. There are some remarkably fine photographs of the cervix and of the uterus and tubes. Finest of all, perhaps, is a remarkable series of pictures showing the progress of an Oxyuris across the appendix on its way to the right abdominal gutter.

Synopsis of Obstetrics. By Jennings C. Litzenberg and Charles E. McLennan. Fifth edition. 403 pages, 163 illustrations. St. Louis, 1957, The C. V. Mosby Company. $6.00.

Litzenberg's now standard *Synopsis of Obstetrics* is attractively produced in a small volume. In it, the succinct—indeed sometimes almost telegraphic—style of its predecessors has been retained; additions and revisions by McLennan have not increased the book's bulk. Virtually all important topics in obstetrics are touched upon to some extent, and with uniform clarity of exposition in spite of the necessarily extreme condensation of style. Considerable emphasis is placed throughout the book on the management of various clinical situations, and although under these circumstances a touch of dogmatism is inevitable, all clinical methods described represent sound and conservative modern practice. Perhaps one of the most commendable features of this book is the consistent attempt of the author to indicate by both spatial arrangement and verbal emphasis the relative importance of the condition being described. The book has been attractively bound, and is printed in a clear type. The illustrations are extremely variable in quality, having been taken from many different sources, including several of the standard textbooks on the subject. Recent advances in obstetric knowledge have been incorporated where appropriate, notably in the chapters on fetal and maternal physiology and injuries and diseases of the fetus.

Atlas of Clinical Endocrinology. By H. Lisser and R. F. Escamilla. 476 pages, 139 plates. St. Louis, 1957, The C. V. Mosby Company. $18.75.

Abnormalities of the human being that result from the improper development of the endocrine glands or their dysfunction are discussed in this atlas. All such abnormalities are included even though some are very rare.

In an effort to portray these conditions properly, photographs of the patients with these disturbances are copiously used. Although the explanations for the causes of many of these abnormalities may vary as more knowledge is acquired, the appearance will not change. Thus an atlas serves a very useful purpose in teaching and may well be more permanent than a textbook.

Although the description of each condition is condensed, it is adequate in most instances for the average clinician. Theories and research investigations are omitted and the laboratory findings are related to the normal so the reader can properly appraise them.

The format is good and makes for easy reading and interpretation.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment. Selected by Phillips Frohman. 564 pages. New York, 1957, Intercontinental Medical Book Corporation with Grune & Stratton. $5.50.

Attention is called to the publication in one volume of selected abstracts appearing during the past year in *The Journal of the American Medical Association.* These have been specifically chosen to illustrate new concepts and therapy. Of the 553 text pages, 229 are devoted to reproduction and another 143 to endocrinology. Thus there are not only presented pertinent advances in obstetrics and gynecology but equally timely abstracts in the other branches of medicine and surgery. The volume is well indexed.

Surgical Gynecology. By J. P. Greenhill. Second edition. 377 pages, 107 illustrations. Chicago, 1957, The Yearbook Publishers, Inc. $9.50.

Sections on preoperative preparation and postoperative care and complications, followed by separate sections on vulvar and perineal operations, vaginal operations, and abdominal operations are contained in this atlas. The second edition includes descriptions and illustrations of several operations which were not included in the first edition, notably lymph node dissection for carcinoma of the cervix, radical vulvectomy and lymph node dissection for carcinoma of the vulva, and a combined vaginal and abdominal operation for prolapse of the vagina following hysterectomy. The method used by the author is to provide a succinct description of the operation on the left-hand page, while on the right-hand page the procedure is illustrated by means of drawings executed by Angela Bartenbach. The operations illustrated are, for the most part, standard procedures in gynecology, although one might question the inclusion in a modern operative gynecology of a description of the Watkins-Wertheim interposition operation for uterine prolapse. The various sections of the book are preceded by drawings of the topographical anatomy of the area to be discussed. As the author emphasizes in his preface, there is no attempt to discuss symptoms, etiology, differential diagnosis, or pathology, the book being designed purely as an atlas of operative technique. Included are descriptions of nongynecologic operations which should be familiar to the gynecologist, including surgical repair of bladder, ureter, and bowel injuries; these are very well illustrated. The section on preoperative preparations and postoperative care and complications has been revised and brought up to date, and is eminently practical in approach, although somewhat short. The book can be recommended as a practical guide for the gynecologist in training, and for the occasional gynecologic operator. It is not likely to be used extensively by the experienced and seasoned gynecologist, whose needs are more elaborate.

BOOKS RECEIVED

The following books were received for review:

Advice to the Expectant Mother. By F. J. Browne and J. C. McClure Browne. Eleventh edition. 48 pages. Edinburgh and London, 1957, E. & S. Livingstone, Ltd.

Gynecologic Surgery and Urology. By Thomas L. Ball. 547 pages, 161 illustrations. St. Louis, 1957, The C. V. Mosby Company. $20.00.

Abdominal Total Hysterectomy. By Frank Musgrove. 32 pages, 18 plates. Springfield, Ill., 1957, Charles C Thomas, Publisher. $2.25.

Human Generation. By Arthur W. Meyer. 143 pages. Stanford, 1956, Stanford University Press. $3.50.

SELECTED ABSTRACTS*

The American Journal of the Medical Sciences

Vol. 233, No. 5, May, 1957.

*Mills, L. C., Handley, C. A., and Moyer, J. H.: Triiodothyronine: Treatment of Hypothyroidism and Effect on Renal Function, p. 546.

*Faloon, W. W., Downs, J. J., Duggan, K., and Prior, J. T.: Nitrogen and Electrolyte Metabolism and Hepatic Function and Histology in Patients Receiving Tetracycline, p. 563.

Mills, Handley, and Moyer: Thiiodothyronine: Treatment of Hypothyroidism and Effect on Renal Function, p. 546.

Twelve patients with hypothyroidism (10 following thyroidectomy) were given DL-triiodothyronine orally in divided doses of 100 to 200 mcg. per day. The blood cholesterol fell very rapidly with initiation of therapy and rose quickly upon cessation. The basal metabolic rate and electrocardiogram changed somewhat more slowly. In the majority of patients the response was the same as to desiccated thyroid, but in 3 there was a further improvement when desiccated thyroid was added to the DL-triiodothyronine treatment. In the 2 subjects studied, the maximal tubular capacity for excretion (Tm PAH) increased without any change in renal plasma flow (RPF) or glomerular filtration rate (GFR).

Ten dogs were given heroic doses of DL-triiodothyronine; 4 were given 4 to 5 mg. the evening before and another 4 to 5 mg. in the morning, several hours before renal function was measured. The other 6 dogs were given 1 to 2 mg. daily for periods of up to a month, and renal function was measured at weekly intervals. In both groups of dogs there was a significant rise in GFR,RPF and maximal tubular capacity for reabsorption of dextrose. These effects appeared more promptly after DL-triiodothyronine than after thyroxin treatment.

L. C. CHESLEY

Faloon, Downs, Duggan, and Prior: Nitrogen and Electrolyte Metabolism and Hepatic Function and Histology in Patients Receiving Tetracycline, p. 563.

Nitrogen balance studies were made in 2 patients who were receiving 2 Gm. of tetracycline orally per day. In 7 patients, liver biopsies and liver function tests were done before and after the administration of tetracycline for periods of from 6 to 19 days. The function tests used were (a) Bromsulphalein retention in 45 minutes, (b) serum bilirubin, and (c) thymol turbidity.

The previously positive nitrogen balance decreased in both cases, becoming negative in one, while the patients were taking tetracycline. In approximations the sodium balance appeared to become positive while the potassium balance became negative (intakes calculated from tables, urinary outputs not measured in one case).

No significant changes were observed in the liver function tests. One patient's liver biopsy showed moderate fatty changes before tetracycline; after 16 days on the drug, there was an increase in fat with the appearance of central necrosis. Five days after discontinuance of the drug, another liver biopsy showed essentially normal structure.

L. C. CHESLEY

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*Titles preceded by an asterisk are abstracted below.

Bulletin of the World Health Organization

Vol. 15, 1956.

*Pasca, M.: Trends of Female Mortality From Cancer of the Breast and Cancer of the Genital Organs, p. 5.

Pascua: Trends of Female Mortality From Cancer of the Breast and Cancer of the Genital Organs, p. 5.

The author reviews the mortality statistics for cancer of the breast in females, and for malignant neoplasms of the uterus and the other female organs, in 19 countries during the years 1920-1953. During the period studied, the mortality from cancer of the breast has increased by more than 100 per cent in Denmark, Italy, Norway, the Netherlands, Sweden, Union of South Africa, Chile, Australia, and New Zealand; and more than 50 per cent in England, Wales, Scotland, Ireland, Switzerland, and in the United States. In Japan, on the other hand, the total mortality appears to be significantly lower. Analysis of the figures by age groups indicates that breast cancer generally plays an insignificant role in mortality statistics before the age of 25, but increases rapidly thereafter. For the same period, the mortality rates for cancer of the uterus have evolved in a totally different manner, having remained more or less stationary in some cases, or having even diminished, as was the case in England and Wales, Scotland, Switzerland, and the United States. The total mortality increases markedly with age, and generally attains its maximum among the older patients. The frequency of cancer of the other female genital organs indicates a tendency to increase in most countries, and in some countries there are noticeable differences between the over-all figures relative to these forms of cancer and those which have specifically to do with uterine neoplasms.

DOUGLAS M. HAYNES

Ginecologia y Obstetricia de Mexico

Vol. 12, No. 67, April 30, 1957.

*Bravo, A. A., Ramos, M. G., Murillo, E. G., and de la Vega: Vaginal Cytology and the Cytology of the Urinary Sediment in Pregnancy, p. 73.

Gallo, D.: Cancer of the Uterine Corpus, p. 94.

Echanove, P. A., Roca, E. P., and Campos, R. P.: Afibrinogenemia in Obstetrics, p. 111.

Contreras, J., and Velasquez, T.: Endometriosis, p. 139.

Gutierrez, L. H.: Management of the Climacteric Syndrome, p. 156.

Bravo, Ramos, Murillo, and de la Vega: Vaginal Cytology and the Cytology of the Urinary Sediment in Pregnancy, p. 73.

Three thousand two hundred and fifty-eight smears of urinary sediment were stained with the standard Papanicolaou technique. These had been obtained from 1,198 pregnant women, both normal and with pathological conditions. No important changes were noted in pre-eclampsia, eclampsia, hydatidiform mole, or placenta previa. They were able to make an early diagnosis 90 per cent of the time. They studied cases of threatened abortion, fetal death in utero, including incomplete abortion and ectopic pregnancy, and also took smears early in labor and found changes which enabled them to predict that a pregnancy would end spontaneously within a week or even three days. These findings were predicated upon a differential count of the cells, acidophilic index, and a karyopyknotic index, plus the presence or absence of staining, cellular devitalization, and agglutination. These smears were also used to follow the response of a pregnancy, i.e., threatened abortion, to therapy. The authors feel that the specimens are easily collected and their use is helpful not only in diagnosing difficuties but in evaluating the intensity of the disorder during pregnancy.

FRANCIS O'BRIEN

Journal of the American Geriatrics Society

Vol. 5, February, 1957.

*Fricke, R. E., and Decker, D. G.: Treatment and Prognosis in Elderly Patients With Cancer of the Cervix, p. 183.

Fricke and Decker: Treatment and Prognosis in Elderly Patients With Cancer of the Cervix, p. 183.

The authors present data altering the standard concept that the 5 year survival rate is poorer in the younger age group than in the older. The comparison was made in patients aged 60 years and more with patients up to, but not including, 36 years of age. Of the 159 patients in the younger group, 53.5 per cent survived for 5 years and 45.4 per cent of 205 older patients survived. In the younger group the treatment was usually surgery and/or radiation. Only 4 per cent of the older patients underwent surgery.

ROBERT C. KNAPP

Journal of Clinical Endocrinology and Metabolism

Vol. 17, May, 1957.

*Salhanick, H. A., Holmstrom, E. G., and Zarrow, M. X.: Biological Activity of 17 Alpha Hydroxyprogesterone in the Mouse, Rabbit, and Human Being, p. 667.

Salhanick, Holmstrom, and Zarrow: Biological Activity of 17 Alpha hydroxyprogesterone in the Mouse, Rabbit, and Human Being, p. 667.

It has been reported that 17 alpha hydroxyprogesterone is 60 times as potent as progesterone in the mouse. In the rabbit, however, the free compound was inactive! Since there seemed to be a species difference, the authors decided to test this compound in human beings. The caproate ester of 17 alpha hydroxyprogesterone has been found to have a more prolonged action than progesterone in the human.

17 alpha hydroxyprogesterone was used on 4 women who had a satisfactory estrogen effect and in all 4 there was no progestational effect. When progesterone was used on the same patients, however, there was a definite progestational effect.

These observations confirm the species difference in response to progesterone and its variants. The difference in response between 17 alpha hydroxyprogesterone and its caproate ester cannot be explained.

J. EDWARD HALL

The Journal of Clinical Investigation

Vol. 36, March, 1957.

*Laragh, J. H., and Stoerk, H. C.: A Study of the Mechanism of Secretion of the Sodium-Retaining Hormone (Aldosterone), p. 383.

Laragh and Stoerk: A Study of the Mechanism of Secretion of the Sodium-Retaining Hormone (Aldosterone), p. 383.

The experiments were done on normal dogs, dogs with diabetes insipidus, and a single human subject with congestive heart failure. Urine extracts were assayed in adrenalectomized rats, and active extracts further purified by paper chromatography and reassayed.

In the dogs, the body electrolytes (and their serum concentrations) were varied by feeding, by peritoneal dialysis, and by dilution (Pitressin and water). In the human subject, the serum electrolytes were varied by mercurial diuretics, and low- and high-potassium intake.

Dietary restriction of sodium or lowering the serum sodium did not induce any significant increase in the excretion of sodium-retaining hormone unless the serum potassium increased concomitantly. Feeding of potassium resulted in an increased excretion of sodium-retaining hormone. "The data support the concept that an increase in the concentration of the serum potassium ion is a stimulus for the secretion of aldosterone."

L. C. CHESLEY

The Lancet

Vol. 2, December 15, 1956.

*Ansell, B., and Clarke, E.: Epilepsy and Menstruation, p. 1232.

Ansell and Clarke: Epilepsy and Menstruation, p. 1232.

The authors collected information regarding the menstrual cycles of female epileptic patients. Sixty-three per cent of the females with epilepsy reported more seizures during menstrual bleeding or during the 24 hours immediately preceding it. This relationship seemed to be equally common in both idiopathic (centrencephalic) and symptomatic groups. The premenstrual tension syndrome was no more common in epileptic than in healthy women: There was no constant relationship between pregnancy and epilepsy, whether there was a menstrual aggravation of seizures or not. Using a radioactive sodium tracer technique, the authors demonstrated that the pattern of sodium metabolism is the same in healthy as in epileptic females, so that alterations of sodium metabolism with consequent retention of water before and during the menstrual period is apparently not a prime factor in the pathogenesis of menstrual epilepsy.

DOUGLAS M. HAYNES

Volume 1, May 11, 1957.

*Strang, L. B., Anderson, G. S., and Platt, J. W.: Neonatal Death and Elective Caesarean Section, p. 954.

*Mattingly, D.: L-Noradrenaline Therapy in Acute Renal Failure, p. 962.

Strang, Anderson, and Platt: Neonatal Death and Elective Caesarean Section, p. 954.

Extending a previous study of the effect on the babies of the cesarean sections that were performed in the Princess Mary Maternity Hospital, Newcastle, during the years 1946-1950 (J. Obst. & Gynaec. Brit. Emp. 60: 264, 1953), the present report is an assessment of the effect of such operations on the babies as they were done in this hospital during the period 1946-1955. Inasmuch as only the effect of the operation per se was to be studied, the following were excluded: stillbirths, "not elective" cesarean sections that were done because of emergencies of all kinds or after prolonged labor, instances of hemolytic disease of the newborn, and maternal complications such as diabetes mellitus, heart disease, antepartum hemorrhage, and eclampsia. Only "elective instances" which included operations performed within a few hours of the onset of labor, cases of disproportion, and some instances of pre-eclampsia were included in this series.

Of 251 mature babies delivered by cesarean section, 5 died, but 3 of these had congenital malformations. The other 2 deaths were caused by unexplained massive pulmonary hemorrhages. One of the latter babies and one of the babies with congenital defects had pulmonary hyaline membranes. Of 36 premature babies delivered by cesarean section, 9 died. Autopsies on 8 of these disclosed severe congenital malformations in 2; massive pulmonary hemorrhage in 2; pulmonary hyaline membranes in 3; and cerebral edema in 1.

The mortality rate is similar to that of premature babies after all forms of delivery in the same hospital (342 deaths in 2,043 deliveries).

In this series, therefore, there was no unusual preponderance of pulmonary hyaline membranes or other manifestations of what has been regarded as the "cesarean section

syndrome." The number of cases of respiratory illness was small (1 mature and 2 premature infants). However, regular respiration was sometimes delayed, presumably because of the anesthesia the mother received. Because of this, all of the babies were handed to a pediatrician immediately and he performed a rapid laryngoscopy and removed by suction any obstructing mucus. The baby was then placed head down and given oxygen until regular respirations were established.

The conclusion is that in this series, which was restricted relative to complications, cesarean section per se does not carry an appreciable extra risk for the baby.

DAVID M. KYDD

Mattingly: L-Noradrenaline Therapy in Acute Renal Failure, p. 962.

Two patients who developed peripheral circulatory failure with hypotension in the course of acute renal insufficiency and who were successfully treated with L-noradrenalin are discussed.

The first, a woman of 63 who developed renal impairment following a vaginal hysterectomy, had marked diarrhea and subsequent hypotension on the third day. She required an infusion containing L-noradrenalin to be administered for 86 hours before the blood pressure became self-sustaining. Diuresis started after 10 days of severe oliguria.

The second, a man of 49, developed acute renal insufficiency in the course of therapy of severe diabetic ketosis. In addition to extensive therapy with insulin and fluids, hypotension was combated by adding L-noradrenalin to the infusion fluids so that he received about 20 μg per minute. Recovery resulted.

The suggestion is made that noradrenalin increases renal blood flow and this more than compensates for whatever local vasoconstrictor action the drug may cause on the renal vessels. The following dosage scheme is proposed: In early circulatory failure, when the systolic blood pressure is greater than 60 mm. Hg, 10 μg noradrenalin per minute; in severe hypotension, 20 μg per minute; when the patient is pulseless, 30 μg noradrenalin per minute should be administered. A nomogram to facilitate the calculation of the dose of noradrenalin is included.

DAVID M. KYDD

Volume 1, May 18, 1957.

*Stott, D. H.: Physical and Mental Handicaps Following a Disturbed Pregnancy, p. 1006.

Stott: Physical and Mental Handicaps Following a Disturbed Pregnancy, p. 1006.

This difficult etiological study of 102 retarded children attempts to define a syndrome that may follow maternal illness or stress during pregnancy. This syndrome may have 3 components: (1) Early ill health of which one or more of the following conditions are characteristic: generally ailing or failing to gain in the first months; subject to nutritional or respiratory disease or local infection; underweight but not under term birth, (2) mental retardation in most cases from birth, (3) congenital malformation. The required data were obtained from the medical histories of the affected children and from interviews with the mothers. These data were compared with those obtained from 450 normal children, either of the same parents (135 children) or of others.

Illness or stress in pregnancy was reported in 66 per cent of the mothers of the 102 retarded children but in only 30 per cent of those of the normal children. Of the 22 malformations found in the combined total of 552 normal and retarded children, 18 were associated with pregnancy troubles. In the retarded group, the adverse factors in pregnancy included 24 instances of maternal illness, of which 12 were toxemia. There were 38 instances of maternal stress (matrimonial trouble, illness, injury, or death of husband or another child, eviction, bombing, etc.).

The proposed explanatory hypothesis depends upon teleological reasoning.

DAVID M. KYDD

Correspondence

Priority in Description of Amniotic Fluid Embolism

To the Editors:

I have read with interest Dr. Martin A. Tuller's paper "Amniotic Fluid Embolism, Afibrinogenemia, and Disseminated Fibrin Thrombosis," published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 73: 273, 1957.

I regret that he has repeated the error of Steiner and Lushbaugh when they claimed to be the discoverers of amniotic fluid embolism.

This syndrome was identified, its mechanism of action elucidated, and its lethal possibilities recognized by my countryman, Juvenal Ricardo Meyer, in a paper entitled "Embolia pulmonar amnio-caseosa," which was published in 1926 (Brasil-medico 2: 301-303), fifteen years before Steiner and Lushbaugh's studies. Juvenal Meyer's paper was correctly included in the *Quarterly Cumulative Index Medicus* of 1927 (vol. I, p. 497).

Together with this letter I am sending you a microfilm of Meyer's paper and one of a personal article in which attention was called to these facts in 1952.

DR. NILO PEREIRA LUZ

DOCENTE-LIVRE DE CLINICA GINECOLOGICA
FACULDADE DE MEDICINA DE PORTO ALEGRE
RIO GRANDE DO SUL, BRASIL
MAY 9, 1957

Study of Eye Grounds in Toxemia

To the Editors:

Attention should be directed again to the great value of careful study of the eye grounds at the earliest appearance of the pre-eclamptic phase of toxemia, usually the elevation of the blood pressure. Such a study can be extremely significant in differentiating transient and essential hypertension from the initial index of toxemia.

It is well known that toxemia may be advanced or advancing with rather rapid progress although the patient may, clinically, appear surprisingly well. On the other hand, though the patient may look or feel ill, the toxemic state may be mild and controllable—at least for a time.

The eye grounds supply an important clue to what may be transpiring in a suspected toxic state. Of course, like any one finding, their condition must be interpreted as part of the whole picture. Yet, evaluated by a trained physician, certain aspects of the retina are astonishingly accurate in diagnosis. The most important of these, and the earliest visible sign of toxemia, is segmental arterial and arteriolar spasm. This may or may not be accompanied by generalized edema. There is an associated elevation of the blood pressure and proteinuria, which may assist in determining the extent of the progress.

In those patients given a trial of bed rest, with or without support, who fail to exhibit a satisfactory fall in blood pressure, there is a typical retinal vasospasm, with or

without blurring of vision. Mild to moderate degrees of interstitial retinal edema may then set in, followed by petechial or flame-shaped hemorrhages; then rupture of the larger vessels, as the severity increases, to the point of flat separation of the retina. At this stage, the mother and baby are unquestionably being subjected to serious impairment. Even then, if the pregnancy is terminated, the eye ground changes may completely disappear, but if the pre-eclamptic stage has been prolonged or if the hypertension is extreme the fundi may exhibit the features characteristic of malignant hypertension. A severe toxemic state can be assumed to be present, when 6 to 7 or more grams of protein per liter per 24 hour urine specimen is lost and yet there may be seen only segmental spasm of the retinal tree. What is going on in the retina is occurring simultaneously in the placenta, brain, and renal bed.

Because of the rapidity with which this disease strikes, and the necessity of taking into account every factor which can contribute to prompt and wise diagnosis and decision, the eye grounds may be a most important guide in evaluation.

MILTON J. FREIWALD, M.D.
DIPLOMATE OF THE AMERICAN
BOARD OF OPHTHALMOLOGY

JEFFERSON MEDICAL COLLEGE
PHILADELPHIA, PA.
MAY 16, 1957.

Items

American Board of Obstetrics and Gynecology

The Part I Examinations of the American Board of Obstetrics and Gynecology are to be held in various parts of the United States and Canada on Thursday, Jan. 2, 1958, at 2:00 P.M.

Candidates notified of their eligibility to participate in Part I must submit their case abstracts within thirty days of notification of eligibility. No candidate may take the Written Examination unless the case abstracts have been received in the office of the Secretary.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office.

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Seventh International Cancer Congress, London, 1958

Those planning to attend the Seventh International Cancer Congress, which will take place at the Royal Festival Hall, London, from July 6 to 12, 1958, are reminded that enrollment forms must be received at the Congress Office (45 Lincoln's Inn Fields, London, W.C. 2) by Jan. 1, 1958, if a late fee is not to be incurred. Registration forms may be obtained from the Secretary-General at that address.

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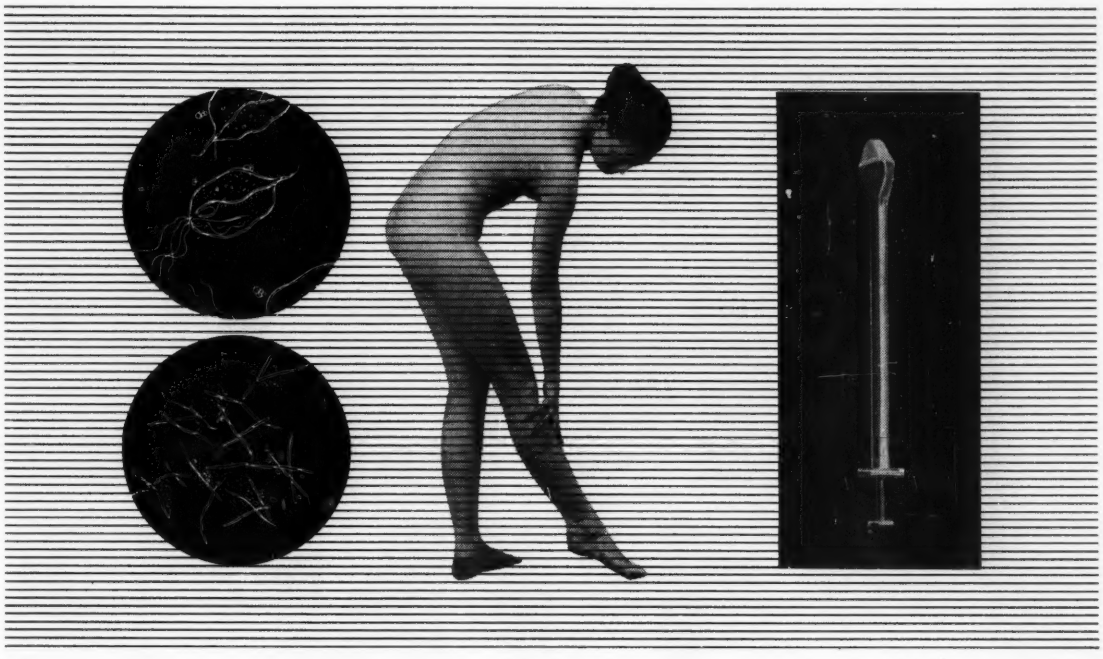

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1. Davis, C. H.: Trichomonas Vaginalis Infections: A Clinical and Experimental Study, J.A.M.A. *157:*126 (Jan. 8) 1955.

2. Pitt, M. B.: Leukorrhea, Causes and Management, J.M.A. Alabama *25:*182 (Feb.) 1956.

3. Lang, W. R.: Recent Advances in Vaginitis, Philadelphia Med. *51:*1494 (June 15) 1956.

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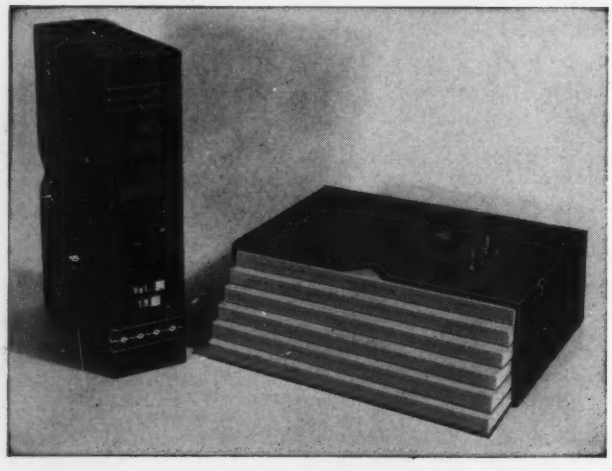

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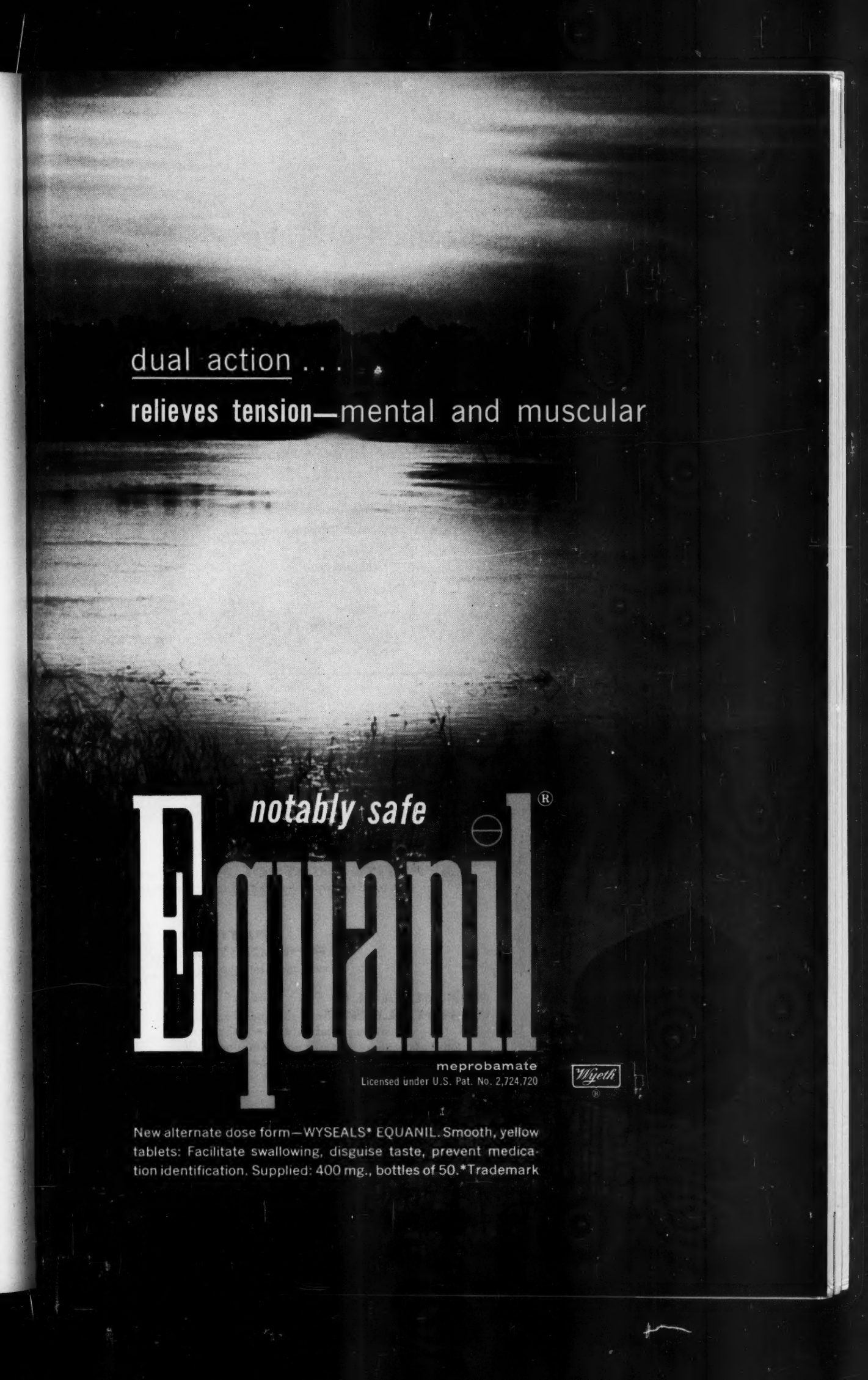
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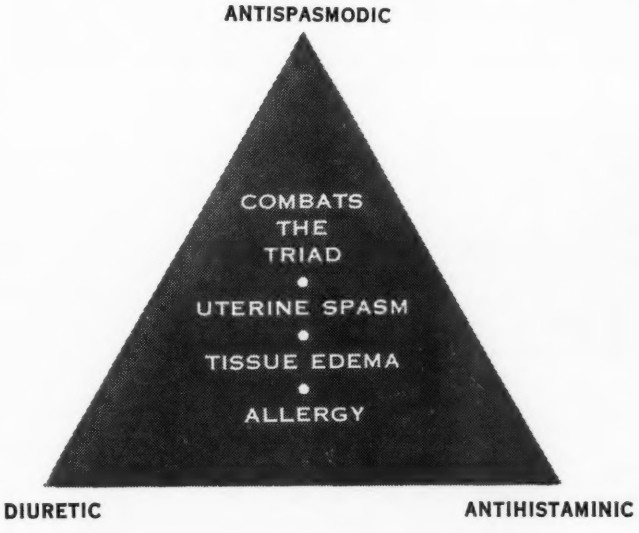

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"Be sure to keep on course, Miss Quimby, for if you get five miles out of the way, you'll be over the North Sea, and you know what that means."

She climbed to 6,000 feet. Freezing cold and still fog.

She pointed her nose down. The comforting clatter of the Gnome engine changed to a coughing splutter. It was conking out! She leveled off, figuring how she'd ditch. To her relief, the engine suddenly took hold. Harriet re-checked her compass.

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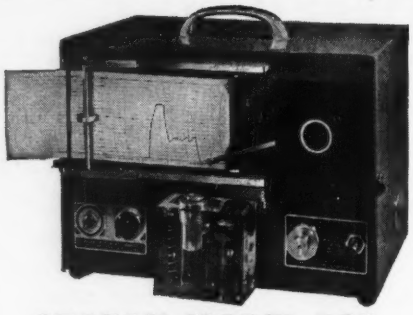

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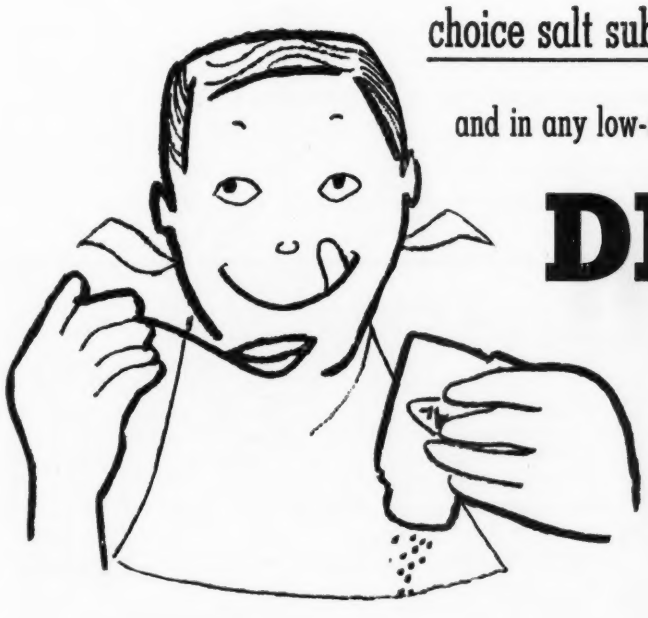

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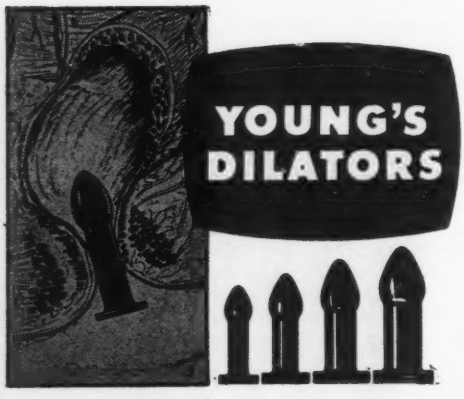

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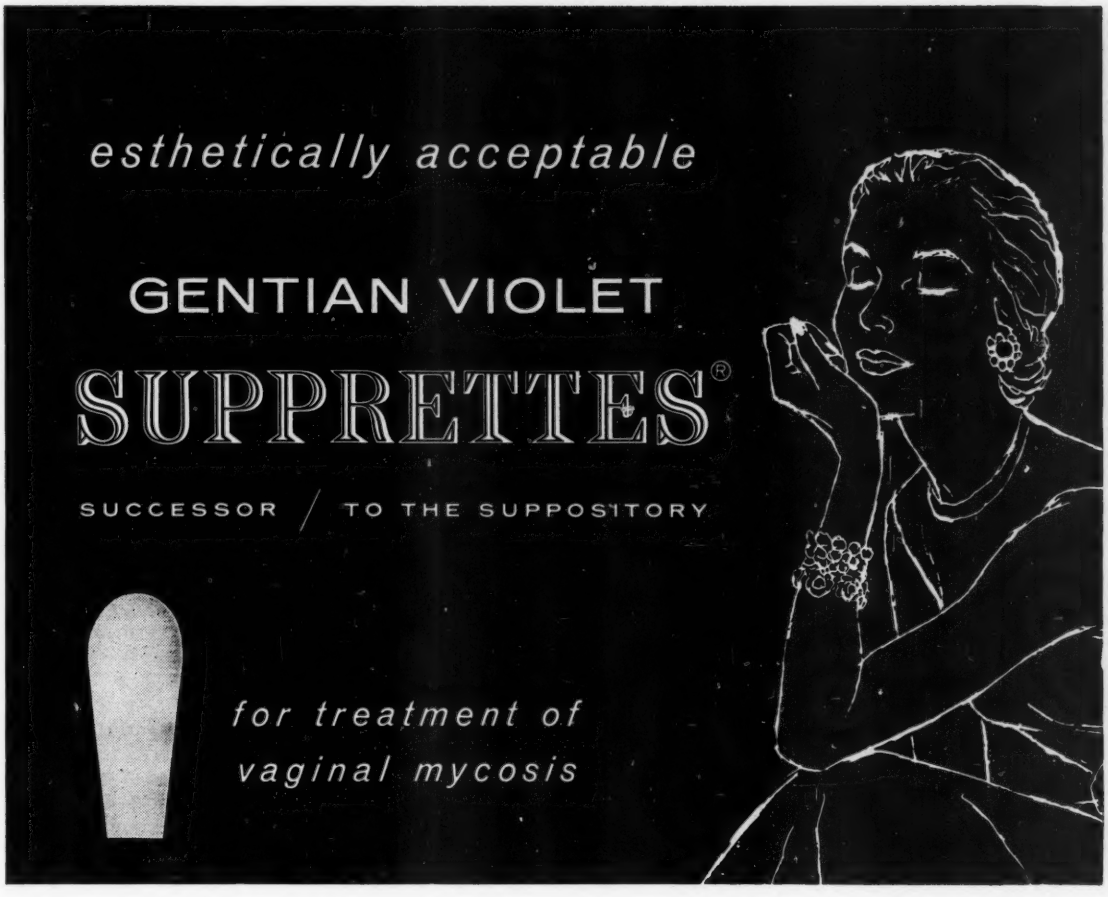

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